ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 17, Number 6 NOVEMBER-DECEMBER, 1933 Serial No. 92

HEMOCHROMATOSIS. II. A REPORT OF THREE CASES WITH ENDOCRINE DISTURBANCES AND NOTES ON A PREVIOUSLY REPORTED CASE. DISCUSSION OF ETIOLOGY

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A decade ago case-reports of hemochromatosis were published as a rarity. Until 1918, only 75 cases of hemochromatosis were described in the entire literature; while between 1918 and 1932, 112 more cases were added. This increase in the occurrence of hemochromatosis is probably only apparent and can be explained by more frequent recognition due to greater familiarity with its manifestations. Our continued interest in hemochromatosis is due to a desire to find a solution of the problems of etiology and pathological physiology which this disease presents.

REPORTS OF CASES

Case No. 4, Hospital No. 62,095. Hemochromatosis; myocardial degeneration; hypogonadism.

F. W., American male, aged 59, single, was admitted to the University of California Hospital on August 3, 1931, with the complaint of "diabetes" and rapid darkening of the skin.

The family history was not relevant.

Past history. The patient was born in Minnesota and lived there until he was 22. Since then he has resided in Montana and California, working as a steam engineer. At the age of 26 the patient had a chancre for which he received intermittent medication by mouth and by inunctions. Fourteen months after the appearance of the chancre he had a swelling of the penis accompanied by a large sore on the scalp and on the back. At the age of 42 a positive Wassermann test was obtained and the patient was given six injections of salvarsan, followed a few years later by four injections of neosalvarsan. There were many attacks of gonorrhea and an inguinal bubo at the age of 43.

The patient complained of slight dyspnea on exertion, and, during the month before entry, had had three attacks of palpitation with precordial discomfort on exertion. He had a chronic cough in the morning with some grayish sputum. Loss of libido six years before.

The patient always drank large quantities of beer (8 to 10 quarts daily). Since prohibition he occasionally drank whiskey, but had taken no alcohol during the preceding year. He needed to shave only twice a week, whereas formerly he had to shave daily.

Present Illness. About 14 years ago friends of the patient noticed that after bouts of drinking, his skin would become dark, and for this reason nicknamed

him "Blackie." Seven years ago the patient visited his old home in Minnesota, where much comment was made by relatives on the darkness of his skin. However, he was subjectively well until one year ago, when he began to experience extreme thirst accompanied by polyuria (about 12 quarts), nocturia (3 to 4 times), weakness, and loss of weight (17 lbs. in 10 days). In addition, there was marked deeping of the cutaneous pigmentation.

The patient consulted a physician who found glycosuria and prescribed a calculated diet with 30 units of insulin a day. At the end of a month he regained 3 pounds in weight and reported marked fading of his pigmentation. Then he began to have insulin reactions, and the dose of this hormone was decreased to 21 units. A year passed uneventfully except that the patient had attacks of diarrhea about every three weeks. These attacks disappeared after minor changes in diet or insulin dosage.

Two weeks ago the patient's physician noticed more marked darkening of the skin and increased the dose of insulin to 28 units. Following this, he had vomiting and diarrhea. One week before entry, fullness of the abdomen and swelling of the ankles were discovered. During the last nine days, according to the patient, the color of his skin deepened daily.

Physical Examination. The patient was a poorly developed man, appearing older than his stated age. His skin was dry and wrinkled over the face, but smooth over the body. There was little subcutaneous fat. A diffuse, bluish, slaty pigmentation was seen over the entire body with the exception of the thighs. The backs of his hands and forearms showed especially marked discoloration. On the back a depigmented scar, 6x10 cm., was present. The mucous membranes showed no abnormal pigment. The hair on the scalp was thin and there was a depigmented scar, 3x4 cm. devoid of hair. The beard was very sparse and soft. There was no hair on the body except a few pubic hairs. Moderate cervical, axillary and inguinal adenopathy was present. The pupils reacted to light only slightly. The retinal arteries were tortuous. The lungs showed poor expansion. The heart was moderately enlarged to the left. All superficial arteries were thickened. The blood pressure was 110/70 mm. of Hg. The abdomen was round and full. Channels of collateral circulation were seen over the abdomen, chest and flanks. A sharp edge of the liver was felt in the right flank at the level of the anterior superior spine. It passed 2 cm. below the umbilicus and extended to the left costal margin in the midclavicular line. A notch 4 cm. deep was felt in the edge of the liver at the right midclavicular line. A tender spleen was palpable 3 cm. below the costal margin. Suggestive evidence of free fluid in the abdomen was obtained. There was a scar in the left inguinal region. The penis also showed a scar 1 cm. in diameter. The testicles were small (2.5 x3.5 cm.) and soft. On rectal examination no prostate was palpable. The legs showed marked varicosities, pitting edema, and partial bilateral fusion of the second and third toes. Upper and lower abdominal reflexes were absent. The knee-jerk was weak on the right side and absent on the left. The Achilles reflex was absent bilaterally. The Romberg maneuver was moderately positive.

Laboratory Findings. (1) Formed elements of the blood: Aug. 3. The hemoglobin was 82 per cent (Sahli) or 11.5 gm. per 100 cc. of blood; the erythrocyte count was 4,150,000 per cu. mm. and the color index was 1.0; the leucocytes numbered 9,000 per cu. mm. with a normal differential count. A smear showed a marked decrease in the number of platelets. On Aug. 8, the platelet count (method of Rees and Ecker) was 100,000 per cu. mm. The clotting time on Aug. 9 (method of Lee and White) was 11 min. The clot was normal. A fragility test for red blood cells showed beginning hemolysis at a concentration of 0.36 per cent and complete hemolysis at a concentration of 0.28 per cent NaCl (no control used). A reticulocyte count gave 0.3 per cent. On Aug. 31 the hemoglobin was 82 per cent or 11.5 gm.; the erythrocytes numbered 3,500,000; the color index was 1.17, and the leucocyte count 7,160 with moderate lymphocytosis. Sept. 8, the hemoglobin was 80 per cent or 11.2 gm.; the erythrocyte count was 3,200,000; the color index was 1.5, and the leucocyte count was 5,700 with a moderate lymphocytosis. Sept. 13, the hemoglobin was 78 per cent or 10.9 gm.; the erythrocytes were 3,500,000; the color index was 1.1, and the leucocytes 5,200 with moderate lymphocytosis. Sept. 15, the platelet count was 130,000 and the bleeding time 3½ min. The fragility test showed beginning hemolysis at 0.36 per cent, with complete hemolysis at 0.28 per cent HaCl (normal control used); the cell volume was 30 per cent (Sahli hemoglobin tube method); the volume index was 1.21; the halometer reading showed the average size of the erythrocytes to be 7.9 microns.

(2) Blood chemistry. On Aug. 4, the blood sugar was 0.274 mg.* The plasma cholesterol was 181 mg. and the NPN 29 mg. per cent. Aug. 11, the icterus index was 12. Aug. 17, the blood sugar was 0.270, and on Aug. 18 it was 0.022 (taken during an insulin reaction). The blood sugar was 0.229 on Aug. 20, and on Aug. 31 it was 0.126. Plasma CO_2 tension was 53 cc., and plasma cholesterol 218 mg. Sept. 5, Calcium of the serum was 10.8 mg. Sept. 14, the blood sugar was 0.277. On Aug. 4 and Sept. 14, the blood Wassermann and Kahn tests gave negative results.

(3) Urine. Aug. 3, on entry sugar was +++; acetone, +; uroblin, ++; sp. gr., 1.018. Aug. 23, no hemosiderin was found in the sediment. Aug. 31, Urobilinogen was +. No hemosiderin granules were seen in the sediment. Sept. 2, no creatine was present in a 24-hour specimen.

(4) Stools. Aug. 7, Large pieces of undigested vegetables were present. The benzidine test for occult blood was ++ (the patient was not on a meat-free diet). On Sept. 7, the stool was normal.

(5) Spinal fluid. Aug. 31, the Wassermann test was ++++ in the first three dilutions. Proteins and globulins were +. The colloidal gold curve was normal. There was 1 lymphocyte per cu. mm.

(6) The basal metabolic rate was plus 14 per cent.

(7) Electrocardiograms. Aug. 3, there was a tendency to left axis deviation, with flattened T_1, flat T_2, inverted T_3. Sept. 16, the major deflections were of low voltage. All T waves were flattened. It was concluded that there was definite evidence of myocardial damage.

(8) Functional tests. On Sept. 15, fractional gastric analysis after an alcohol-meal and histamine gave normal results. On Aug. 27, the Rose Bengal liver function test showed, at the end of 8 minutes, 71 per cent, and at the end of 16 minutes 43 per cent of the dye in the blood (upper normal limits are 50 per cent at 8 minutes, 30 per cent at 16 minutes). Aug. 30, after 8 minutes, 71 per cent, and after 16 minutes, 41 per cent of the dye was present in the blood. It was concluded that there was considerable impairment of the excretory function of the liver. On Aug. 29, renal function tests were made. Volhardt concentration test gave normal results. The phenolsulphonephthalein test showed 40 per cent in two hours (25 and 15 per cent).

(9) X-ray examination of the chest on Aug. 5 showed cardiac enlargement of the left ventricular type, chronic bronchitis and chronic pleurisy. On Aug. 31, gastro-intestinal x-ray examination showed marked periduodenal adhesions.

(10) On Aug. 7, biopsies (report on pathology by Dr. D. Deng and Dr. E. I. Bartlett) showed with the Prussian Blue stain, granules of hemosiderin in the corium especially about the sweat glands; in the axillary lymph node hemosiderin granules were present in the phagocytic cells and in the reticular cells of the sinusoids.

Course in the Hospital. The patient came to the hospital with mild diabetic acidosis. Treatment by weighed diet and insulin revealed marked fluctuations of the level of blood-sugar and of the amount of sugar excreted in the urine. Frequent hypoglycemic reactions were observed. Numerous changes in the diet and insulin dosage could not remedy this state of affairs. Two weeks after entry the patient commented on the fading of his cutaneous pigmentation. This was confirmed by members of the staff. The edema of his ankles cleared up. Six weeks after admission the patient was discharged, weighing 51 kgm., on a diet of 2400 calories (carbohydrate 200 grams, protein 95 grams, fat 135 grams) and 80 units of insulin.

After leaving the hospital the patient went back to his work and was carefully weighing his diet and taking insulin. In view of persistent hypoglycemic reactions which occurred at various times of the day, the dose of insulin was decreased to 60 units. Three weeks after discharge, he developed marked edema of the ankles, ascites, and numerous coarse râles at the bases of both lungs. This was reflected in a gain of 5 kgm. in weight.

A week later the patient contracted a lower respiratory infection and had an attack of unconsciousness which came on 10 minutes after the morning injection of insulin and lasted for about three hours. Intravenous administration of glucose did not terminate this attack. Three days later he had a similar attack in the evening lasting for 1½ hours. Coincident with the first attack of unconsciousness there was noted epigastric pain, increased dyspnea and distension of the abdomen.

*All specimens of blood were obtained on the fasting stomach unless otherwise stated.

Second Entry. Hospital No. 62,571, October 16, 1931. The physical examination was as previously noted. In addition, a further increase in the size of the heart, and pulsating veins of the neck and upper extremities were found. Examination of the blood and urine gave no new information.

On the third day of his second entry, the patient had two attacks of absolutely irregular heart action with a pulse rate of between 68 and 140. Pressure over the eyeballs and on the vagus nerve produced no change in the cardiac rate. One and a half hours after the onset of the second attack he expired.

Clinical Diagnosis. Hemochromatosis with cirrhosis of the liver; pigmentation of the skin; diabetes mellitus; myocardial degeneration with congestive failure and auricular fibrillation; hypogonadism; syphilis with early tabes dorsalis; syndactylism of the lower extremities.

Autopsy was performed by Dr. H. Blackfield 16 hours after death. *Anatomical Diagnosis.* Hemochromatosis; generalized hemosiderosis, particularly involving the heart (Fig. 1), pancreas, hypophysis (Figs. 2 and 3), thyroid gland (Fig. 4), adrenals, liver, spleen, and skin; hypertrophic, finely nodular biliary cirrhosis; diffuse sclerosis of the pancreas and myocardium; genital hypoplasia; anasarca; chronic passive congestion of lungs, spleen, etc.; mild generalized arteriosclerosis.

Case No. 5, Hospital No. 57,501. Hemochromatosis; auricular fibrillation; hypogonadism.

L. S., Jewish male, aged 43, single, entered the University of California Hospital on October 8, 1930, complaining of weakness, shortness of breath and loss of weight during the preceding six months.

The family history was not relevant.

Past History. The patient was born in New York and has been a sailor most of his life. Seven years ago he spent a few weeks in the Philippine Islands and in China. With the exception of an attack of gonorrhea contracted 18 years ago, he was never sick until ten years ago when he had recurrent pleurisy which was diagnosed as tuberculosis. Exophthalmos was noted at about the same time. Two years ago the patient underwent, in another hospital, an operation for adenoma of the thyroid (see pathological report). At the time of the operation he was found to have auricular fibrillation which has persisted to date. The urine contained no sugar.

He had had palpitation, rapid heart rate and gaseous distension for two years.

His habits were very irregular. He smoked tobacco and used coffee in excessive amounts. Until five years ago the patient drank one pint of whiskey daily for four years, but has had little alcohol since.

Present Illness. About five years ago the patient began to notice gradually increasing pigmentation of his ankles which spread upward. Nocturia began during the same period. Six months ago he began to lose weight rapidly and lost a total of 19 kgm. At the same time there appeared weakness and a constant thirst compelling him to drink "at least three gallons of water a day." This resulted in polyuria (every ½ to 1 hour, day and night). The patient's appetite, which descreased at first, soon became enormous. Recently he has complained of orthopnea.

Physical Examination. The patient was a dusky, emaciated man, with great respiratory distress. The skin over the legs showed a striking, almost black pigmentation which was deepest over the ankles. The mucous membranes were free from pigment. The hair showed no abnormalities. Cervical, axillary and inguinal lymph nodes were enlarged. The eyes were prominent and lid lag was present. The fundi showed increased white lines on the arteries. Upper and lower plates were present in the mouth. The thyroid gland was barely palpable. The pulse was absolutely irregular (rate 132) and there was a pulse deficit (cardiac rate 196). Blood pressure was 132/84. The superficial veins of the abdomen were dilated, especially on the right side. The liver was enlarged, and its sharp edge was palpable at the level of the umbilicus. There were several large furuncles on the back. A coarse tremor of the fingers was present.

Laboratory Findings. (1) Formed elements of the blood. On Oct. 8, the hemoglobin was 81 per cent or 11.3 gm.; the erythrocyte count was 4,740,000; the color index 0.86; the leucocytes 12,040 with a normal differential count. On Oct. 14 the leucocytes numbered 9,200.

(2) Blood-chemistry. On Oct. 8 (3 hrs. after lunch) the sugar was 0.516; on Oct. 9, it was 0.258, and on Nov. 2, 0.190.

(3) Urine. On entry, Oct. 8, sugar was ++++; acetone, +; albumin, faint trace. On Oct. 15 there was much intracellular and extracellular hemosiderin in the sediment.

(4) Sputum examination on Oct. 14 showed no tubercle bacilli.

(5) Stool examination on Oct. 21 gave negative results.

(6) The basal metabolic rate on Oct. 12 was plus 18 per cent.

(7) The Rose Bengal test for hepatic function on Oct. 16 showed at the end of 8 minutes 52 per cent and at the end of 16 minutes 30 per cent of the dye in the blood. It was concluded that the excretory function of the liver was at the lower limit of normal.

(8) X-ray examination of the chest showed changes indicative of mild arteriosclerosis, chronic bronchitis and emphysema, and pleural thickening over the right apex.

(9) Biopsies (report on pathology by Dr. A. H. Heald and Dr. E. I. Bartlett). On Oct. 13, large, blue-staining hemosiderin granules were present in greatest numbers in the cytoplasm of phagocytic cells around sweat glands and about the walls of arterioles in the skin. Occasional fixed connective tissue type of cells contained red hemofuscin granules in addition to hemosiderin. There was no evidence of an old or recent inflammatory reaction. In the axillary lymph node the Prussian Blue reaction showed occasional extracellular blue granules, indicating the presence of hemosiderin.

The pathology report by Dr. C. L. Connor on a section of the thyroid gland removed two years ago indicated an essentially normal thyroid gland with slight colloid storage. There was no pigmentation.

Course in the Hospital. This patient came to the hospital with mild diabetic acidosis and was put on a weighed diet and insulin. During his stay in the hospital he developed a bronchopneumonia but recovered from it. After this the normal cardiac rhythm was restored by means of quinidine. The patient, who weighed 53.6 kgm., was discharged on a diet of 2980 calories (carbohydrate, 225 grams; protein, 70 grams; fat, 200 grams) and 40 units of insulin. Adjustments of the diabetic regime were made according to the appearance of sugar in four daily specimens of urine. No attempt was made to bring the blood sugar down to the normal level.

Three weeks after discharge, auricular fibrillation again set in. Treatment of the patient's diabetes in the Out-Patient Department was otherwise uneventful for 3½ months. Blood sugar at that time was 0.148 (3½ hours after breakfast).

Soon after his last visit to our clinic, Mr. S. entered the U. S. Marine Hospital and has been there since as an ambulatory patient. He was visited by one of us on February 3, 1932. At that time the patient weighed 61 kgm. and was receiving a diet of 2187 calories (carbohydrate, 159 grams; protein, 84 grams; fat, 135 grams) and 54 units of insulin. His fasting blood-sugar was 0.163 and the urine contained from 0.5 to 1 per cent of sugar. In spite of this, there were frequent insulin reactions. The cardiac rhythm was kept normal by the administration of quinidine. The pigmentation of the skin and the size of the liver had remained unchanged.

Mr. S. was seen again on January 28, 1933. He had gained 8 kgm. in weight and was receiving the same diet and dosage of insulin. His fasting blood-sugar was 0.240. He passed daily 1.5 to 2 liters of urine which usually contained as high as 1.2 per cent of sugar (rarely 2.2 per cent) and no acetone. In recent months the patient had had only two hypoglycemic reactions and both could be accounted for by his failure to eat part of the preceding meal. The pigmentation over his legs had diminished considerably. On the other hand, new deposits of a dark, bluish pigment had appeared bilaterally on the buccal mucosa along the line of closure of his artificial denture. The cardiac findings were unchanged. On 0.2 gm. of quinidine daily the rhythm of the heart remained normal with a rate of about 80 and essentially normal electrocardiographic findings. When the quinidine was tentatively discontinued one month ago, the patient relapsed into auricular fibrillation, but promptly responded again to the drug. An electrocardiogram taken during this episode showed the usual findings of auricular fibrillation with an auricular rate of 180 and frequent ventricular extrasystoles. The blood pressure was 128/82.

The size of the liver had markedly diminished so that its edge extended only 2 cm. below the costal border. A Rose Bengal test of hepatic function which we were able to perform through the courtesy of the Medical Director of the Marine Hospital, Dr. M. J. White, showed a retention of 55 per cent and 28 per cent of the dye, respectively, at the end of 8 and 16 minutes. It was con-

cluded that the excretory function of the liver had not changed in the last 2½ years. The patient's libido had markedly decreased during the past year and his testicles were softer than normal. There were no changes in the amount and distribution of hair.

Present Status. Hemochromatosis with cirrhosis of the liver; pigmentation of the skin; diabetes mellitus; hypogonadism; auricular fibrillation; bronchopneumonia.

Case No. 6, Hospital No. 59,683. Hemochromatosis; myocardial degeneration; pre-adolescent eunuchoidism.

J. G., Italian, male, aged 21, single, entered the University of California Hospital on March 9, 1931, with the complaint of shortness of breath on exertion, and swelling of abdomen and feet.

The family history was not relevant.

Past History. The patient was born in Oakland, California, and worked in a drug store. He had had the usual childhood diseases. In 1919 a severe attack of influenza with pneumonia kept him in bed for two months.

Since this illness the patient's growth and development had been arrested. His voice had not "changed." He had never had sexual desire or seminal emissions.

His habits were not remarkable, except for the custom of drinking wine with meals. This had been taken only rarely during the past year. He had never had to shave.

Present Illness. Since the attack of influenza the patient always had been weaker than other boys of his age. About two years ago a dusky color of his skin was noticed. One and a half years ago he consulted Dr. H. G. MacLean of Oakland for dyspnea on exertion. The physician observed at that time bronzing of the skin and the face, cardiac enlargement with auricular fibrillation (pulse rate 110), arterial hypotension (B.P. 88/60), and enlargement as well as tenderness of the liver. Digitalis and rest in bed produced marked improvement which lasted until shortly before entry. Six weeks ago the patient had a recurrence of dyspnea and noticed marked swelling of his abdomen. He was given three injections of Novasurol but only the first had the desired effect.

Physical Examination. The patient was a poorly developed youth appearing to be about 15 years of age. The skin was smooth and fine in texture. A diffuse greyish-brown pigmentation of the extremities, especially marked over the arms, was somewhat masked by cyanosis which was most noticeable in the lips and nails. The mucous membranes were not pigmented. There was complete lack of body hair, and fat pads were seen over the hips and pubis. A few cervical lymph nodes were palpable. The tonsils were hypertrophied and infected.

Examination of the heart revealed marked enlargement, and an irregular rhythm with rates varying between 26 and 79 per minute. A systolic murmur was heard all over the precordium. There was dullness to percussion and limited expansion at the base of the right lung, and coarse râles were heard at the bases of both lungs. The abdominal veins were dilated. The liver was greatly enlarged and extended below the level of the umbilicus. It was pulsating and had a rounded edge. There were no signs of ascites.

The genital organs were infantile. On rectal examination the prostate was barely palpable and no seminal vesicles were felt. There was slight edema of the ankles.

Body Measurements. The height was 164 cm.; the arm span, 168 cm.; upper measurement (from head to pubis), 73 cm., and lower measurement (from pubis to soles), 91 cm.

Laboratory Findings. (1) Formed elements of the blood. On March 9, the hemoglobin was 88 per cent or 12.3 gm.; the erythrocytes were 4,610,000; the color index 0.96; the leucocytes 7,450 with a normal differential count. The Wassermann test was negative.

(2) Routine urine examination on March 9 gave negative results, and on April 8 it was negative for hemosiderin.

(3) Stool examination on March 9 gave normal findings.

(4) The basal metabolic rate on March 23 was minus 15 per cent.

(5) A glucose tolerance test on March 14 gave a normal curve. The Rose Bengal test on March 7 showed that at the end of 8 minutes 56 per cent and at the end of 16 minutes 35 per cent of the dye was detected in the blood. It was concluded that the excretory function of the liver was somewhat impaired. In a modified glucose tolerance test, the blood sugar curve went to a minimum

of 0.028 mg. per cent at the two-hour period while the patient had a hypoglycemic reaction. It was concluded that there was marked impairment of the carbohydrate-metabolism-regulating function of the liver.

(6) Electrocardiograms taken on five occasions showed complete auriculoventricular block with ventricular extrasystoles (ventricular rate 34 to 38). In the first electrocardiogram the auricles were in a state of flutter (rate 246); in the remaining four the auricular contractions were normal (rate 62 to 76).

(7) X-ray examination of the chest on March 11 showed cardiac enlargement, particularly of the left ventricle; chronic passive congestion of the lungs; atelectasis of the right lower lobe possibly from pressure on the bronchus. On March 14 x-ray examination of the skull gave negative findings. On March 19 x-ray examination of the pelvis and extremities showed failure of the following bones to unite: Heads of the femur and of the greater trochanter (normally at 17 years); epiphyses of the phalanges and metacarpal bones of the hands (normally at 18 years); distal epiphyses of the radius, ulna and femur; proximal epiphyses of the tibia and fibula (normally at 20 years). It was concluded that the bone-age was below 17 years. On March 30 an x-ray examination of the chest showed that the density at the right base was almost gone. Also, the signs of congestion of the pulmonary fields were less.

(8) Biopsy (Pathology report by Dr. E. I. Bartlett). The sweat-glands after staining with the Prussian Blue showed deposits of hemosiderin in the tunica propria.

The patient was treated for chronic passive congestion with digitalis and other measures with great improvement. Diminution in cyanosis revealed more clearly the cutaneous pigmentation. An attempt to break the heart-block with novatropine medication was unsuccessful. The patient was discharged on a maintenance dose of digitalis.

Clinical Diagnosis. Hemochromatosis with cirrhosis of the liver; pigmentation of the skin; myocardial degeneration with complete heart-block, paroxysmal auricular flutter and chronic passive congestion; and hypopituitarism with preadolescent eunuchoidism.

The patient died from congestive heart failure two weeks after leaving the hospital. There was no autopsy.

FOLLOW-UP NOTES ON A CASE OF HEMOCHROMATOSIS WITH HYPOGONADISM

Since Mr. D. O'L. was reported (1) (our Patient 3), he has been followed in the Out-Patient Department for six years. His diet was gradually increased from 1841 calories (carbohydrate, 106 grams; protein, 73 grams; fat, 125 grams) to 2430 calories (carbohydrate, 180 grams; protein, 90 grams; fat, 150 grams) one and a half years after discharge from the hospital, without change in the dosage of insulin (55 units). Sixteen blood-sugar-determinations taken three hours after breakfast varied from 134 to 342 mg. per cent, but only three of these were below 216 mg. In spite of this and of moderate excretion of sugar in the urine, he continued to have frequent mild to moderate hypoglycemic reactions, often two a day, which responded to several lumps of sugar. During the last year the hypoglycemic reactions have been less frequent. The tendency to formation of acetone bodies previously described has practically disappeared. No further decrease in the pigmentation of this patent's skin was noted, so that while the color of his face and arms is almost normal, the legs are still quite dark. There have been no changes in the size of the liver, the extent of the collateral circulation, or the functional capacity of the heart. Libido has not returned and no new growth of hair was noted. During the six and a half years since his first admission, the blood pressure increased from 96/70 mm. to 115/60 mm. In the same period of time the Rose Bengal test for hepatic function showed a decrease in dye retention at the end of 16 minutes from 45 to 35 per cent. During the first five years, Mr. O'L. gained 15 kgm. in weight but in the course of the last year he lost 7 kgm. In recent months he began having large purpuric spots on his hands and feet, and also some bleeding from the gums. Throughout this time the patient was able to hold his position as night watchman.

DISCUSSION

Etiology. During the last four years much experimental work has been done in this country and in Germany in an effort to clarify the etiology of hemochromatosis by reproducing it in animals. The increasing

incidence of this disease is an inducement to clinicians to utilize the knowledge gained from this experimental work and from new clinical observations for purposes of prevention and treatment.

Hemolysis. When the nature of the pathological changes in hemochromatosis was first described, its cause was naturally thought to be excessive hemolysis. Later this view was more or less abandoned for lack of clinical evidence indicating increased blood-destruction or regeneration. Some newer observations again suggest the possibility of a causal connection between hemolysis and hemochromatosis.

Increased destruction of erythrocytes is known to cause siderosis in man and animals, but it is pointed out (2) that the sites of deposition of blood-pigment in cases of siderosis differ from those in hemochromatosis. This objection fails to take cognizance of the fact that the distribution of pigment differs not only in various types of anemia which are partially or wholly dependent on abnormal hemolysis, but also from one case of hemochromatosis to another.

Rous and Oliver (3) observed a pigmentation strikingly similar to that of hemochromatosis but without cirrhosis, in rabbits which had been given repeated transfusions of foreign red blood corpuscles. Since other investigators did produce simple cirrhosis of the liver through excessive hemolysis induced by the administration of hemolytic sera or of phenylhydrazine (4, 5, 6, 7), the absence of hepatic cirrhosis in the animals of Rous and Oliver might be explained by insufficient duration of their experiment.

Mallory and Parker (8) who, by poisoning animals with copper, caused a widespread pigmentation and cirrhosis of the liver, discovered that the acute effects of copper include destruction of erythrocytes as manifested by hemoglobinuria and subsequent anemia, increased blood regeneration, and hyperplasia of the bone marrow.

Contrary to the earlier concepts, there is also some clinical evidence of increased blood destruction in hemochromatosis. Kühl (9) demonstrated in a case of this disease increased destruction and regeneration of erythrocytes taking place in cycles of four to five days. His conclusions are based upon a quantitative study of the excretion of urobilin in the urine and feces, the consumption of oxygen by the red blood cells, and the morphological characteristics of erythrocytes after supravital staining. Hess and Zurhelle (10) and Rindfleisch (11) reported cases of hemochromatosis with hemoglobinuria. Chalier and Nove-Josserand (12), Villaret, Justin-Besançon and Even (13), and Wood and Fitz-Hugh (14) found subnormal resistance of red blood cells in their cases. In addition, Blanton and Healy (15) reported that hyperplastic changes of the bone-marrow are usually found in hemochromatosis. Finally, the frequently observed disproportionate enlargement of the left lobe of the liver (1, 14), which receives blood largely from the spleen, may be explained by hypertropic changes due to increased amounts of pigment coming from this organ.

Copper. In 1921, Mallory, Parker and Nye (16) revived interest in experimental poisoning with copper, a subject which has been intermittently investigated since the researches of Ellenberger and Hofmeister (17) in 1883. From their experiments, Mallory, et al., concluded that by feeding acetate of copper they could produce, in several species of animals, cirrhosis of the liver with pigmentation of parenchymatous organs resembling hemochromatosis. This theory of the etiology of hemochromatosis was extended to man and supported by eliciting from several patients suffering with the disease a history of industrial exposure to copper. In addition, Mallory (18) showed that some samples of illicitly distilled liquor contain a considerable amount of this metal.

Flinn and Von Glahn (19), Polson (20), Oshima and Siebert (21), Herkel (22), and Andrianoff (23) were unable to reproduce the experiments of Mallory. Later, Mallory and Parker (8) again produced a condition closely resembling hemochromatosis in rabbits by injecting metallic copper subcutaneously. Hall and Butt (24) and Hall and MacKay (25) obtained similar results with oral administration of copper acetate.

Approaching the same question from a different angle, Herkel (22) compared the content of copper in livers from patients with and without hemochromatosis. He found that 12 normal livers contained between 6 and 36 mg. of copper per kg. of dry substance. In 24 cases of hemochromatosis the content of copper in the liver varied from 42 to 348 mg. per kg. In eight of 10 cases of hepatic cirrhosis without hemochromatosis, the copper was increased to the same extent (68 to 375 mg. per kg.). Herkel also found that the liver of normal infants contains many times the amount of copper present in adult livers. From these data he concluded that copper probably has some function in all actively proliferating tissues and for this reason is found in increased amounts in the livers of infants and of patients with different types of cirrhosis.

Two natural experiments which are taking place in different parts of the world bear an interesting relation to the rôle of copper in the etiology of human hemochromatosis. One of us (T.L.A.) was told in Freiburg, Germany, of the unusual frequency of hemochromatosis in the adjacent Black Forest. Further inquiry revealed that the local peasants, who make their own wine, were protecting the grape vines from molds by spraying them with copper sulphate. This appeared to be an important fact in favor of Mallory's theory. However, the significance of this evidence is somewhat invalidated by the habitual consumption of much alcohol and the frequent inbreeding among the population of the valleys of the Black Forest. The importance of these factors will be considered later.

The second natural experiment was reported by Mills (26), who investigated the incidence of hemochromatosis in Korea, where brass cooking vessels are in general and almost exclusive use. The Koreans use various articles of food which could act as solvents of copper, e.g., sour pickles, sauerkraut, and vinegar. In spite of the custom of leaving food in these

brass vessels, often for days, Mills found no hemochromatosis in Korea. Considering the possibility that the local physicians might not be familiar with this disease, he studied statistically the frequency of diabetes on the supposition that patients with undiagnosed hemochromatosis, if numerous, might swell unduly the ranks of the diabetics. However, he found less diabetes mellitus in Korea than is known to exist in the United States.

In evaluating the part played by copper in the production of hemochromatosis in man the following facts must be remembered: (1) Exposure to copper was established only in a few cases of this disease; (2) thousands of individuals who are equally exposed to this metal never develop hemochromatosis; (3) relatively enormous doses of copper are required to produce cirrhosis with pigmentation even in rabbits which, as a species, are susceptible to hepatic lesions (27). The daily dose equivalent to that used by Hall and MacKay, and in part by Mallory and Parker, namely, about 0.2 gm. of copper per kg. of weight, would amount in human beings to about 14 gm. as compared to the usual daily ingestion of 3 to 5 mg. While copper may play an etiologic rôle in some cases of hemochromatosis it probably is not the only cause of this disease.

Alcohol. Another possible cause of hemochromatosis is alcoholism. The fact that a majority of the reported cases of this disease are chronic drinkers strongly supports this view. In the series of 61 cases collected by Bork (28) almost two-thirds of the patients were chronic alcoholics.

It is true, as shown by Mallory, that strong alcoholic beverages can be contaminated with copper through unskilled distillation. On the other hand, hemochromatosis existed in the United States before prohibition when distillation was done in large plants built for this purpose; and it also occurs in Europe. Moreover, some patients with hemochromatosis overindulged, not in distilled liquors, but in beer or wine. However, the occurrence of hemochromatosis in total abstainers shows that alcohol also cannot be the only cause of this disease.

Rôle of the Liver. In considering the etiology of hemochromatosis, the status of the liver must be carefully examined because, excepting abnormal metabolism of iron pigments, hepatic cirrhosis is the only constant feature of the disease. In this connection, Rous and Oliver (3) made the important observation that "when tendency to siderosis exists an intercurrent cirrhosis (of the liver) will greatly increase the deposits of pigment." The liver is known to play an important part in the intermediary metabolism of blood-pigments, and there are conditions other than hemochromatosis in which hepatic insufficiency appears to be responsible for disorders of this metabolism. For instance, depletion of the glycogen in the liver results in pathological urobilinuria (29). Another example is hematoporphyrinuria, in which hepatic damage is associated with the excretion of abnormal pigments. (30). Borst and Königsdörfer (31) reported a case of congenital hematoporphyrinuria in which deposits of iron pigment resem-

bling those of hemochromatosis were found in all organs. The frequent presence of hematoporphyrin in the urine of patients with hemochromatosis (9 and 32) shows further the close relationship of various disturbances of pigment-metabolism to each other and to the liver.

It is considered significant that all noxae which have been regarded as etiological agents of hemochromatosis are also causes of hepatic cirrhosis. A number of poisons such as copper, zinc, arsenic and lead are known to cause necrosis of hepatic cells. It is hardly accidental that these metals which are known to cause cirrhosis of the liver have also been named as etiological agents in hemochromatosis. The well-established connection between alcohol and cirrhosis of the liver (33, 34) need not be discussed here.

Gye and Purdy (35) produced experimental cirrhosis of the liver by injection of a chemically inert substance, colloidal silica, which is used to block the reticulo-endothelial system. A form of cirrhosis caused by particles of coal, although rare, sometimes occurs clinically and is known as cirrhosis anthracotica (36). Albot (37) found that injections of colloidal silica and of India ink cause hyaline degeneration of the hepatic parenchyma. Since necrosis of hepatic cells is a necessary precursor of cirrhosis of the liver (33), the observations of Albot explain how cirrhosis can be caused by chemically inert substances. Blood pigments, after disintegration of erythrocytes, are also taken up by cells of the reticulo-endothelial system and thus excessive hemolysis probably acts on the liver as injections of colloidal silica in eventually producing cirrhosis. Hall and MacKay (25) also found the earliest pathological changes in their rabbits, subjected to poisoning with copper to be in the Kupffer cells, the hepatic component of the reticulo-endothelial system.

In addition, hemochromatosis and other diseases of the liver have in common a familial tendency which is as yet little understood. This tendency is noticeable in the following reports from the literature. Wegener (38) described a family in which the paternal grandfather died from a disease of the liver; the father had a gray discoloration of the skin and died of a hepatic disease; two brothers had typical hemochromatosis; and three more brother showed gray pigmentation of the skin. Boland and Curran (39) published the case histories of two brothers who had hemochromatosis. Miller and Heimark (40) reported the case of a patient with hemochromatosis whose brother was bronzed even more markedly and in whom also a diagnosis of hepatic disease was made. The father of these men, Scottish by birth, and a sister also had an unusually dark skin. Fritsch (41) attended a man with hemochromatosis who had seven siblings with dark pigmentation of the skin. In addition to pigmentation, two of the brothers also had cirrhosis of the liver. Uhlenbruck (32) reported the case of a patient with hemochromatosis whose son, uncle and three cousins were suffering from hepatic diseases. Eusterman (42) treated a patient with hemochromatosis whose brother died from cir-

rhosis of the liver and who also had had some pigmentation of the skin. Siebert (43) described two cases of hemochromatosis in the same family. Finally, Dworak (44) described a patient with hemochromatosis, whose mother died of hepatic disease. Considering the rare occurrence of hemochromatosis, the sketchy character of many case histories, and the relatively recent awakening of interest in hereditary studies of disease, this is an imposing series of cases indicating a familial predisposition to involvement of the liver in patients with hemochromatosis.

The existence of such a familial tendency, accentuated by much inbreeding in the valleys of the Black Forest, may be responsible for the unusual frequency of this disease around Freiburg. The common occurrence of achondroplasia and other endocrine disturbances in the same region lends support to this possibility.

Of further significance is the fact that there is nothing characteristic about the hepatic cirrhosis in hemochromatosis except the presence of large amounts of hemosiderin. The liver may be hypertrophied and weigh over 3,000 gm., or it may be atrophied and weigh only 1,000 gm. The liver in ordinary cirrhosis, like that of hemochromatosis, usually contains increased amounts of copper and also the iron-containing pigment, hemosiderin (45), although the latter is present in smaller amounts. Moreover, both diseases occur predominantly in males and appear usually in middle life.

Several conclusions can be drawn from the reviewed facts bearing on the etiology of hemochromatosis. The rarity of the disease and the presence of a familial tendency suggest a strong constitutional predisposition in individuals who become victims to it. This predisposition, which is probably connected with an organ-inferiority of the liver, develops under the influence of certain toxins into a perversion of the blood-pigment metabolism. The latter in its turn contributes to the production of hepatic cirrhosis. Any toxic agent affecting the susceptible organ or organs responsible for hemochromatosis may bring about the clinical realization of the inherent predisposition. At present the most frequent immediate cause of hemochromatosis appears to be chronic alcoholism.

Clinical Picture: Etiology. Excessive use of alcohol for many years was admitted by two of our patients. In one of these cases beer, and in the other whiskey, was the preferred beverage. The third patient, according to the Italian custom, was in the habit of drinking wine with his meals. No contact with copper or other hepatic poisons was elicited in these cases. There was also, as far as our investigations went, no evidence of excessive blood destruction or regeneration.

Pigmentation of the Skin. All three of our pateints stated that pigmentation of the skin was noticeable before the onset of any other symptoms. In the first case the history of pigmentation was unusually interesting. The dark color of the skin in this patient was observed by his friends

14 years before entry into the hospital. At that time he temporarily became dark after drinking bouts, and, for this reason, was nicknamed "Blackie." To our knowledge, such transient pigmentation has never been described in hemochromatosis, but we do not doubt the patient's statement, especially since we have ourselves observed diminution of pigmentation in this, and two other, cases. Moreover, it has been shown that, even in normal individuals, a single large indulgence in alcohol will cause temporary derangement of pigment-metabolism, expressed in a rise of bilirubin in the blood and in increased urobilinogen excretion in the urine (46).

Seven years later, Mr. F. W.'s pigmentation must have become permanent because on a visit East his relatives made much comment on the darkness of the patient's skin.

One year before admission and simultaneously with the onset of symptoms related to diabetes, the pigmentation became intensified. It is of interest that one month after the patient was put on a calculated diet with insulin, the pigmentation had faded considerably. His skin was again noticed to have become darker two weeks before entry, as he became generally worse. During the last nine days before hospitalization, the patient claimed to have been getting perceptibly darker every day.

In the hospital a deep, slaty pigmentation of the entire body, with the exception of the thighs, was noted. A biopsy of the skin showed hemosiderin in the typical location around sweat glands in the corium.

Two weeks after Mr. F. W. was given a weighed diet with an increase in the dose of insulin, he called our attention to a diminution in the intensity of his pigmentation. This was confirmed by all staff members who had seen him shortly after admission.

Of the remaining patients, pigmentation of the skin had been observed in one five years and in the other two years before admission to the University of California Hospital. In both cases the extremities were more highly pigmented than the rest of the body, and biopsies of the skin showed numerous granules of hemosiderin around the sweat glands. Treatment for diabetes did not appreciably affect the degree of pigmentation in Patient 5 for the first year and a half. However, during the last year, considerable fading took place. The other patient had no diabetes.

The pigmentation of our Patient 3, D. O'L., reported six years ago, also diminished considerably after he was placed on a weighed diet with insulin, but did not disappear entirely. After several months the degree of pigmentation became stationary and has remained unchanged to date.

This improvement in the metabolism of pigments, which is known to be closely connected with the liver, may be explained by increase of hepatic glycogen induced by the diabetic regime. This explanation is offered because, in the first place, the glycogen content of the liver in hemochromatosis is low; in the second place, insulin has a favorable influence on the deposition of glycogen in the diabetic liver; in the third place, replenish-

ment of hepatic glycogen improves the functional capacity of the liver in general, and its ability to handle pigments, in particular (47).

Only one of our patients (No. 5) showed pigmentation of his buccal mucosa which is evidence of melanosis, if we accept the general concept that hemosiderin is never deposited in mucous membranes. Melanosis has been reported in hemochromatosis as part of a mild Addison's syndrome due to fibrosis of the adrenal glands, following large depositions of hemosiderin. The fact that the pigmentation in the mouth has appeared while the patient's skin had been fading, appears to favor a different origin of the buccal pigment. On the other hand, his blood pressure is normal and there has been no downward trend to confirm the suspicion of adrenal insufficiency. The future clinical course may give a more definite answer to this question.

The other two patients had a low blood-pressure, but no pigmentation of the mucous membranes, even though Patient 4 was later found to have rather heavy deposits of hemosiderin in the adrenal cortex. It is of interest that the systolic blood pressure of Patient 3 was 20 mm. higher after six years of observation than at the time of his hospital entry.

Cirrhosis of the Liver. Since hepatic cirrhosis is an invariable feature of hemochromatosis, its obvious presence in these patients was of material assistance in diagnosis. In all three cases the liver was enormously enlarged and collateral circulation was in evidence.

In Patient 4 splenomegaly and an icterus index of 12 served as confirmation of the diagnosis of hepatic cirrhosis. In Patient 5 the liver underwent much shrinkage during the last year of observation. The results of Rose Bengal liver function tests show that there had been no diminution in the excretory function of this organ during the two and a half years of observation.

Hepatic function tests were also valuable in Patient 6, in whom the presence of cardiac failure was a confusing factor. The positive outcome of both the Rose Bengal and the modified glucose-tolerance tests in this boy shows that chronic passive congestion accounted for only part of the hepatic enlargement.

In Patient 3 the size of the liver and the extent of the collateral circulation have remained stationary during six years of observation, while the ability to excrete Rose Bengal was somewhat improved at the end of this period.

Diabetes Mellitus. Six years ago we first had occasion to describe the most important characteristic of diabetes in hemochromatosis, namely, a pronounced instability of the blood-sugar-regulating mechanism with frequent hypoglycemic reactions whenever an attempt is made to bring the sugar of the blood near the normal level. Since then many clinicians have confirmed these observations; and our explanation that probably insufficient storage of glycogen in the damaged liver with limited possibilities

for release of glucose is responsible for this phenomenon, still appears to satisfy the known facts. To this we can now add from observations on the metabolism of carbohydrates in expermental hepatic damage (48), the factor of reduced glyconeogenesis due to cirrhosis.

A case of hemochromatosis recently reported by Yater, McNabb and Horgan (2) demonstrates very well this instability of the blood-sugar-regulating mechanism, even in the absence of exogenous insulin. Their patient was given orally 100 gm. of dextrose in the course of a sugar-tolerance test. The fasting blood-sugar was 107 mg. per cent. The blood-sugar at the two-hour period was 167 mg., but it must have been much higher in the interval because the corresponding specimen of urine gave almost complete reduction of Benedict's solution. At the three-hour period the blood sugar was only 42 mg., showing that the liver in this case was unable to release enough dextrose to counteract the increase in endogenous insulin stimulated by the administration of sugar. A similar but more striking phenomenon was described as a spontaneous and regular occurrence by Wagner and Parnas (49) in a girl with simple cirrhosis of the liver. This patient had postprandial hyperglycemia, amounting at times to 430 mg., yet in the morning the amount of sugar in her blood often was too small for quantitative determination. This case is of special interest to us because, in the absence of hemochromatosis, with its manifold possibilities of affecting other glandular organs, the involvement of the liver can be regarded as the sole cause of the instability of the blood sugar. Moreover, failure of epinephrine injections to raise the blood sugar of this patient is direct evidence of insufficiency of hepatic glycogen.

Moderately severe diabetes was found in two of the three new cases of hemochromatosis reported here. Instability of the blood sugar with frequent hypoglycemic reactions was observed in both cases, in spite of high fasting blood-sugar and almost constant excretion of sugar in the urine. Our old Patient 3, D. O'L., continued to show the same peculiarities, but there also was a considerable increase in carbohydrate-tolerance, a virtual disappearance of the tendency to acidosis, and, during the last year, also a decrease in the frequency of hypoglycemic reactions. This improvement in the patient's carbohydrate metabolism is probably to be ascribed to a moderate recovery of the liver which is also reflected in an increase of the excretory power of this organ.

The tendency to acidosis, so outspoken in our Patient 3, due probably to the more advanced stage of the disease, was not prominent in the two other patients. Wood and Fitz-Hugh (14) have also described a patient with hemochromatosis who had a similar tendency to formation of acetone bodies.

A third peculiarity of diabetes sometimes seen in hemochromatosis is resistance to insulin, to which attention was first called by Allan and Constam (50), and which, since then, has been frequently mentioned in reports of this disease. We are in hearty agreement with Root (51) in that, when

speaking of "insulin-resistance," a distinction must be made between patients with severe diabetes where large doses of insulin are needed and patients who are refractory to this hormone in the sense that they require more insulin than patients with so-called "total diabetes." This distinction is important because the diabetes of hemochromatosis is often severe and may progress rapidly. A good case in point is the patient of Stetson and Peters (52) who had no diabetes on entry to the New Haven Hospital, developed hyperglycemia and glycosuria a month later, had to be given insulin ten weeks after admission, and required 120 units of insulin daily on the same diet three months after insulin was first started. Another indication of the severity of diabetes in this case was the high nocturnal rise in blood sugar which was noted three months after the onset of diabetes.

Root points out that in diabetic coma a temporary need of 200 to 500 units of insulin does not constitute resistance to this hormone because some patients with simple diabetes require as much and yet several days later need less than 50 units daily. According to this author, 100 units of insulin a day for a considerable period, without insulin-reactions or without the expected action on the blood-sugar, is a minimum requirement to justify the diagnosis of insulin-resistance. This figure is by no means high, if we are to accept Root's calculation of the insulin requirements of a hypothetical totally depancreatized human being, which he places at between 200 and 300 units a day.

Judged by these standards only four published cases of hemochro matosis (14, 38, 50 and 51) can be said to have exhibited resistance to insulin, so that it cannot be considered a frequent occurrence in this disease.

The whole subject of resistance to insulin is well covered by the article of Allan and Constam and that of Root. From these papers it becomes clear that insulin resistance is by no means limited to hemochromatosis, but may occur in a variety of diseases. The mechanism by which the usual action of insulin is prevented differs, depending on the clinical aspects of the case. In hemochromatosis it probably is through the failure of an unknown activity of the liver which is necessary for the proper functioning of insulin. This theory was suggested by the occasional occurrence of insulin-resistance also in simple cirrhosis and in tumor of the liver (50).

The discovery of Markowitz (53) that dehepatized dogs are refractory to insulin supports this view. The fact that all four patients with hemochromatosis, who were truly resistant to insulin, developed this condition shortly before death, can be interpreted as the beginning of a terminal functional failure of the liver.

Cardiac Involvement. Our three newer patients had in common prominent cardiac symptoms. Major disturbances of rhythm were present in all cases. Patient 4 had Stokes-Adams' attacks during which he lost con-

sciousness for periods from 1½ to 3 hours. His heart beat at such times was absolutely irregular, with a rate varying between 68 and 140. The possibility that these attacks were due to hypoglycemia was ruled out by the fact that they were unrelieved by intravenous administration of dextrose. Patient 5 had had auricular fibrillation for at least two years prior to admission. During his stay in the hospital the normal rhythm was restored by quinidine medication, but the patient relapsed into fibrillation whenever this drug was discontinued. Patient 6 exhibited complete auriculoventricular block which proved refractory to novatropine. His auricles usually beat in the normal fashion, but on one occasion they were found to be in a state of flutter. The ventricular rate varied from 26 to 74 and ventricular extrasystoles were present.

In addition to disturbances of rhythm, Patients 4 and 6 had marked enlargement of the heart with chronic passive congestion. The first of these men died a cardiac death in the hospital during one of his Stokes-Adams' attacks. The second succumbed to congestive heart failure two weeks after his discharge.

Remarkable in all three cases was the absence of the usual causes of cardiac disease. Our first patient had syphilis, but at autopsy no luetic lesions were found in the heart. Large deposits of hemosiderin in the cardiac muscle was the only possible cause brought to light by the pathological examination (Fig. 1). It is interesting that the skeletal muscles

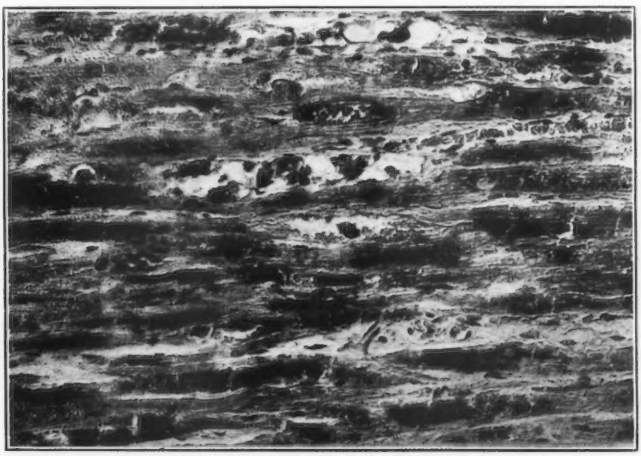

Figure 1. Section of the cardiac musculature in Patient No. 4, exhibiting marked perinuclear deposition of hemosiderin. X220. Prussian blue stain.

of this patient were entirely free from pigmentation. The second patient had been subjected to thyroidectomy, supposedly for adenoma, and at first this seemed to account for his auricular fibrillation. However, examination of preparations from his thyroid gland, which was removed at an-

other hospital, showed an essentially normal microscopic picture. In this way we eliminated the only plausible cause of this patient's arrhythmia besides hemosiderosis of the heart. In the third patient the only possible but improbable factor which might have influenced the heart besides hemochromatosis was a severe attack of pneumonia from which the family dated the onset of his illness.

Several writers mention the presence of cardiac enlargement and of chronic passive congestion in cases of hemochromatosis, while hemosiderosis of the cardiac musculature appears to be a very frequent finding in this disease. It was found in 33 of 40 recent cases which we reviewed. However, so far, cardiac failure has not been considered an outstanding feature of the clinical picture of hemochromatosis. An explanation for this may be that most patients with hemochromatosis died in the pre-insulin days from diabetic coma. At present, if the diabetes is properly handled, they eventually succumb to some other complication of their disease. It remains for the future to show whether heart failure is going to take a prominent place among the lethal complications of hemochromatosis, other than diabetes. From the cases reported here, this seems quite possible.

Hypogonadism. In our first paper we described two, and reviewed three more, cases of sexual hypoplasia apparently connected with hemochromatosis. In the present series we again have three instances of it. Mr. F. W. suffered a loss of libido at the age of 53, six years before entry. His skin was very smooth. The hair on his face was sparse and required shaving only twice a week. There was also absence of body-hair except for a few scattered hairs at the base of the penis. The patient's testicles were small and soft, and no prostate could be felt on rectal examination. Mr. L. S. presented no evidence of hypogonadism when the diagnosis of hemochromatosis was made, but two years later, at the age of 45, his libido had markedly decreased and the testes had become abnormally soft. The case of Mr. J. G. is particularly interesting because his gonads were affected before puberty. At the age of 21 his voice remained high-pitched, and he never had had sexual desire or seminal emissions. The patient's skin was of fine texture and there was total absence of hair on the face and body. His genitalia were infantile and the prostate was very small. No seminal vesicles could be made out. There were fat pads over the hips and pubis.

We are fortunate in being able to present some interesting evidence in regard to the etiology of hypogonadism in two of these patients. In Patient 4 the testicles at the post-mortem examination appeared smaller and softer than normal. Microscopically, the seminiferous tubules were hypoplastic, but there were no deposits of hemosiderin. On the other hand, the anterior portion of the hypophysis was almost entirely destroyed and replaced by hemorrhage, except for a rim of cells at the periphery and a few cords at the junction of the anterior lobe with the intermediate por-

tion. The cells of the pars nervosa and intermedia did not appear unusual. The remaining glandular cells contained huge amounts of hemosiderin. The same pigment was also present throughout the degenerated part of the anterior lobe (Figs. 2 and 3).

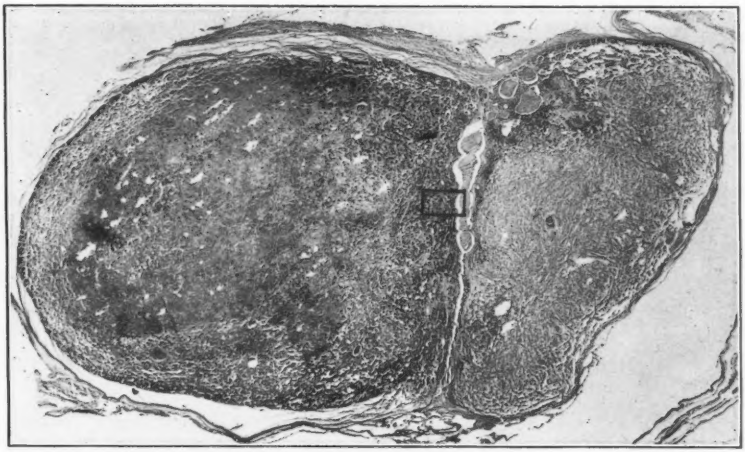

Figure 2. Saggital section through the hypophysis of Patient No. 4. The major part of the anterior lobe is degenerated. An incomplete rim of cells, laden with hemosiderin, remains. X12. Prussian blue stain.

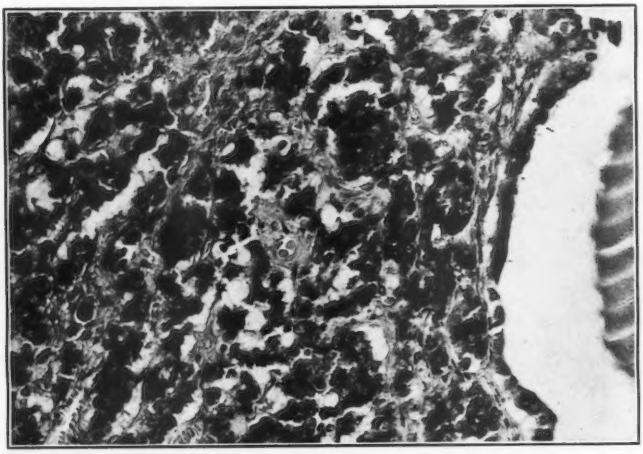

Figure 3. Indicated detail of the anterior lobe of the hypophysis in Case No. 4, showing heavy intracellular deposits of hemosiderin. X220. Prussian blue stain.

In Patient 6 the findings also point to involvement of the anterior lobe of the hypophysis. Failure of the patient to grow after the age of 15 years, in spite of an open state of epiphyseal lines which should have closed normally between the ages of 17 and 21 years, indicates insuffi-

ciency of the growth hormone of the anterior lobe. The obvious eunuchoidism in this case is due to a concomitant deficiency of the sex hormone, which is also secreted by the anterior lobe of the hypophysis. We know from the literature (54) that insufficiency of one of these hormones is always accompanied by an insufficiency of the other. If involvement of the gonads in this case were primary, we would expect overgrowth of the long bones so characteristic of preadolescent castration. On the contrary, our patient ceased growing at 15 years of age, and his measurements confirm this statement. In the last case, since no autopsy was performed, we cannot be certain that hemosiderosis of the hypophysis brought on insufficiency of the secretion of its anterior lobe. It is possible that the attack of pneumonia was responsible.

Since the publication of our previous paper, 12 cases of hemochromatosis with probable hypogonadism in males have been reported in the literature. The salient features are given below in chronological order, under the names of the authors:

Wegener (38). Patient 1, aged 50 years. The testicles were atrophic. The prostate was very small and there was total loss of body hair, except a little on the pubis. Patient 2, aged 41 years. Loss of libido had occurred three years before examination. The shape of the body was eunuchoid. The skin was feminine in type—smooth and soft. There was total absence of hair on the body.

Wood and Fitz-Hugh (14). The patient was 48 years of age and had four children. Loss of libido was reported. The configuration of the face was feminine and the voice was high-pitched. There was no axillary or thoracic hair. The pubic hair was scanty and of feminine distribution.

Keith and McNair (55). The patient was 48 years of age. Loss of libido was reported.

Siebert (42). Patient 1 was 53 years of age. There was absence of body hair. Patient 2 was 52 years old. There was loss of hair on the body. On microscopic examination hemosiderin was found occasionally in walls of blood vessels. In both cases there were heavy deposits of hemosiderin in the hypophysis.

Higgins and Pitts (56). The patient was 47 years old. The hair was thin and very scanty over the head, eyebrows, axillae, and pubis.

Labbé, Boulin, Azerad and Uhry (57), also Labbé, Boulin and Petresco (58). Patient 1 was 38 years old. Loss of libido was reported. The testicles were small and soft. There was almost complete loss of hair over the body and pubis, and diminution of hair on the face and scalp. Upon microscopic examination of the testes it was found that seminiferous tubules as well as interstitial cells were filled with hemosiderin. There was abundant intracellular hemosiderin in the anterior lobe of the hypophysis. Patient 2 was 61 years old. Diminution of libido was reported. The testicles were small and soft. There was total loss of hair. Patient 3 (quoted case of Oberndorfer) was 53 years of age. There was advanced atrophy of the testicles.

Bezançon, de Gennes, Delarue, and Oumansky (59). The patient, age 20 years, came under observation for advanced cardiac failure of unknown etiology, with dyspnea, intense cyanosis, edema and ascites. Symptoms began two years prior to admission. The patient had never had erections. He had a childish face without facial hair. The skin was smooth and fine. There was no axillary or pubic hair. The penis and testicles were very small, and the prostate hypertrophied. Upon microscopic examination great amounts of pigment were found throughout the heart. Serial sections of the valves, papillary muscles, and intraventricular septum revealed no other lesions. The testes showed advanced atrophy and much pigmentation. There was adenomatous hypertrophy of the prostate with discrete pigmentation. The hypophysis was normal.*

*Apparently no special studies for hemosiderin were employed in the study of this case (59). In our Patient 4 the hemosiderin granules in the hypophysis were so fine as to be almost invisible, even through the microscope, until a solution of ferric ferrocyanid was applied, when the section turned dark blue to the naked eye.

The last case is particularly interesting to us because our Patient 6 showed almost an exact counterpart. We regret that no statement is made regarding the skeletal condition of this young man.

Of the three patients with hemochromatosis and sexual hypoplasia cited in our previous paper, one had hemosiderosis of the testes and hypophysis, while in the other two the testicles were free from pigment. In addition to human cases, Taylor, Steven and Reid (60) reported the occurrence of hemochromatosis in a depancreatized cat, the testicles of which showed complete aspermia.

In order to obtain more information on the relative frequency of pigmentation in the testes and the hypophysis, we reviewed a large number of cases of hemochromatosis without hypogonadism. Among 24 patients in whom data on the testes were given, hemosiderin never occurred in these organs outside of the blood vessels and there only in small amounts. All eight patients in whom the hypophysis was examined had considerable deposits of pigment in the anterior lobe.

To summarize the reviewed and our own cases, sexual hypoplasia was found in 20 out of 115 cases of hemochromatosis reported since 1918. This incidence of about 18 per cent would probably be found to be much greater if this condition were looked for. Eighteen of these patients had sexual regression and two were preadolescent eunuchs. In several cases of hemochromatosis with hypogonadism the testes contained very little hemosiderin. On the other hand, the absence of hemosiderosis of the hypophysis was reported in only one case with hypogonadism.

From these data it is seen that hypogonadism is not an uncommon complication of hemochromatosis. Furthermore, we can conclude that hemosiderin has a greater affinity for the hypophysis than for the testes and that in hemochromatosis, sexual hypoplasia is due in some cases unquestionably, and in most cases probably, to involvement of the anterior lobe of this gland.

Other Manifestations of Hemochromatosis. Recently, Stetson and Ferris (61) reported pupura in two cases of hemochromatosis, and called attention to the fact that purpura or hemorrhagic manifestations have been observed in 15 per cent of the reported cases of this disease. Since in both of their cases, dietary deficiency of fruits and vegetables over a considerable period of time preceded the onset of symptoms, these authors suggested that hemochromatosis may predispose to scurvy. This paper aroused our special interest in the recent appearance of bleeding from the gums and the development of large purpuric areas on the hands and feet of our Patient 3. In contrast to the patients of Stetson and Ferris, our man has been on a well-balanced diet which included ample amounts of vegetables and fruits, so that we did not feel justified in making a diagnosis of scurvy. Purpuric manifestations in hemochromatosis may con

ceivably be due to a systemic disorder originating, perhaps, in the liver, or to local injury of capillaries from deposits of hemosiderin.

Like our Patient 3, both new patients with diabetes had increased basal metabolic rates of plus 14 per cent and plus 18 per cent, respectively. As pointed out in our earlier paper, a decrease in the metabolic rate is the usual finding in moderately severe diabetes. Since the acini of the thyroid gland in our Patient 4 contained many intracellular granules of hemosiderin (Fig. 4), an almost universal finding in cases of hemochromatosis

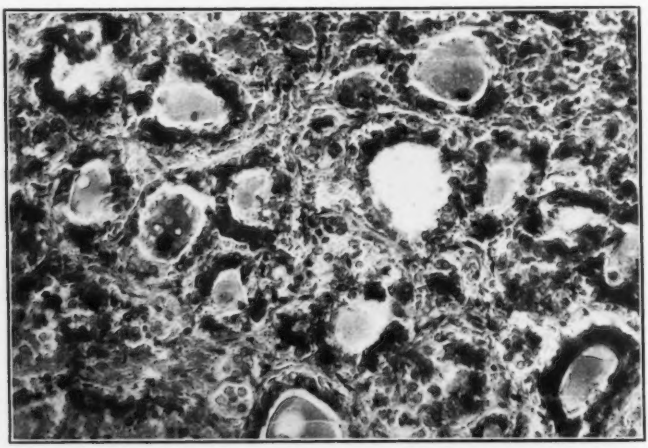

Figure 4. Section of the thyroid gland in Case No. 4. The acini show mild hyperplasia with considerable intracellular hemosiderosis. X220. Prussian blue stain.

where this gland was examined (19 out of 23 reviewed cases), the question arises whether the presence of minute foreign bodies may not irritate the secreting cells to increased activity. The histological picture of mild thyroid hyperplasia in this case lends support to this possibility. If so, this could account for the relatively high basal metabolic rates observed in our cases. This explanation does not conflict with the conception that large deposits of hemosiderin interfere with the efficiency of glandular organs, as for example, the pancreas, because there are other instances where small amounts of a substance stimulate an organ, whereas, larger amounts of the same substance depress it. Such is the action of many hepatic toxins on the liver.

Patients 4 and 5 had cervical, axillary and inguinal lymphadenopathy. In both cases a biopsy revealed the presence of hemosiderin. In Patient 6 only the cervical lymph nodes were enlarged.

The finding of much extracellular and intracellular hemosiderin in the urinary sediment of Mr. L. S. testifies to the presence of considerable deposits of this pigment in his kidneys.

There were no significant symptoms referable to the gastro-intestinal tract in any of these cases.

Results of Therapy. Treatment by insulin, weighed diet and rest, delivered all three of our patients from diabetic acidosis. Patient 3 has been followed for six and a half years, and, during this time, his tolerance to carbohydrate increased and the tendency to acidosis and hypoglycemic reactions diminished. The diabetic status of Patient 5, with whom we kept in touch for two and one-half years, remained unchanged except for a marked decrease in the frequency of hypoglycemic attacks. Both men gained in weight and have no subjective complaints. Mr. D. O'L. has been able to follow his occupation as night watchman. Mr. L. S. is prevented from exercising his vocation because, as a sailor, he would be unable to observe a diabetic regime.

Pigmentation of the skin definitely decreased during the period of observation in three of our patients. The excretory function of the liver has increased somewhat in one case and has remained stationary in the other. The functional capacity of the heart has remained unchanged in both patients. The only new symptoms are purpuric manifestations in Patient 3 and loss of libido with softening of the testicles in Patient 5.

Our observations may be summarized by stating that the disease, which in its natural course is progressive, has been arrested at least temporarily in two of our patients, with some signs pointing to an improvement of the underlying disturbance of the metabolism of iron-pigment. This improvement we ascribe to the favorable effect of the diabetic regime, which, by restoring the normal utilization of carbohydrates, permits renewed storage of glycogen in the liver. In our discussion of the etiology of hemochromatosis, we already have commented on the unfavorable influence of low hepatic glycogen on the metabolism of pigments. We feel that the same factor, namely, increased storage of glycogen, also accounts for the improved stability of the blood sugar level in our patients by preventing hypoglycemic reactions through the release of dextrose from the glycogen of the liver.

In order to relieve the injured liver as much as possible from the task of transforming non-carbohydrate material into dextrose and, at the same time, to insure an ample supply of carbohydrate to the body, it is advisable in handling the diabetes of hemochromatosis to prescribe diets containing a liberal allowance of starches. In addition, we do not attempt to lower the blood sugar below 200 mg. per cent for the sake of avoiding frequent hypoglycemic reactions. As discussed in our previous paper, a moderately high blood sugar appears to be harmless. In cases of hemochromatosis without diabetes, a high carbohydrate diet, with supplementary feeding of dextrose (from 150 to 300 gm. daily) is indicated (47).

Besides our own, there are on record two cases of hemochromatosis with diabetes which were observed for a number of years. The first is a patient of Allan and Constam (50) who, at the end of five years, was still active as a railroad baggage man. The second is the patient of Keith and McNair (55), who was diagnosed to have hemochromatosis in 1918, had a

hospital entry for diabetic coma in 1921, and died from carcinoma of the liver in 1927. For the last four years of his life this man was on a diet containing 2200 calories with 30 units of insulin.

Such cases show that the prognosis of hemochromatosis, even with diabetes, is not always bad and that it may be compatible with the pursuit of an occupation.

SUMMARY

1. Three new cases of hemochromatosis with endocrine disturbances and a supplementary report on a case described six years ago, are presented. The literature on hemochromatosis is reviewed in regard to some new aspects of the disease.

2. Excessive hemolysis, poisoning with copper, chronic alcoholism, and hepatic dysfunction are discussed as possible etiologic agents of hemochromatosis. The conclusion is reached that two conditions are necessary to produce hemochromatosis: a constitutional predisposition of the liver or possibly some other organ; and a chronic intoxication affecting the susceptible organ. The most frequent toxic agent appears to be alcohol.

3. Instability of the blood sugar level is the cardinal feature of the diabetes in hemochromatosis. It is due to insufficient storage of glycogen and reduced glyconeogenesis in the liver. Resistance to insulin in hemochromatosis is rare and, when present, apparently develops as a terminal event. Cardiac failure due to hemosiderosis of the myocardium threatens to become a prominent lethal complication of hemochromatosis. Sexual hypoplasia is present in nearly one-fifth of the patients with hemochromatosis. Deposition of hemosiderin in the anterior lobe of the hypophysis, rather than direct involvement of the gonads is a probable cause of this condition in most cases. Hemosiderosis of the thyroid gland may be responsible for the increase in basal metabolism found in some cases. Treatment for diabetes in the absence of fatal complications brings about improvement of many phases of the metabolism of carbohydrates in hemochromatosis, and may be followed also by diminution of cutaneous pigmentation and improvement in hepatic function. The diabetic regime in this disease should include a liberal allowance of starches; and no attempts should be made to reduce the blood sugar below 200 mg. per cent.

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A CASE OF HYPOPHYSEAL DWARFISM (NANOSOMIA PITUITARIA) PROBABLY DUE TO CYST OR BENIGN NEOPLASM ORIGINATING IN RESIDUES OF THE DUCTUS CRANIOPHARYNGEUS; DISCUSSION OF THE PROBABLE FUNCTIONS OF THE DIFFERENT TYPES OF CELLS OF THE ADENOHYPOPHYSIS

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Thanks to the great advances in clinical studies of endocrinology and metabolism, in studies of the histology, physiology, chemistry, and pathology of the endocrine glands, and in our knowledge of the vegetative nervous system and of genetics made during the past few decades, we are now far better able than ever before to interpret the significance of certain abnormalities of growth, development and maturation that we meet with in medical practice and to arrive at plausible surmises regarding their pathogenesis. Experimental work upon animals has helped us enormously in the acquisition of this new knowledge, but we must always remember that human beings differ in many ways from the animals used in experiments in laboratories, and that the results of laboratory experiments, highly as we prize them, should not be transferred without great caution to the interpretation of our observations in human beings. Accurate clinical examinations controlled by surgical operation or by pathological anatomical studies after death are just as important as they ever were for the advance of knowledge. Reliable ideas of human physiology and pathology can be formed best through very careful correlation of studies of human beings (alive and dead) with studies made upon animals by laboratory experimenters. In the case here described, we can be fairly certain that we are dealing with definite endocrine deficiencies, especially of parts of the hypophysis cerebri, but we must be careful in our attempts at explanation not to go farther than is permitted by the facts thus far at our disposal.

EPITOME OF CASE HISTORY

The patient, Leonard H., age 24, came under observation in the out-patient department (Dr. J. H. Pleasants) of the medical service in April 1932, where careful physical, roentgenological, ophthalmological and endocrine examinations were made, because of underdevelopment, severe headaches, frequent urination and weakness of the left knee. The whole course of this patient's malady has been carefully studied since by Dr. John E. Howard. Dr. T. B. Futcher, interested in the nature of the underdevelopment, discussed the case at one of his clinics to students of the third year. In October, 1932, the patient spent three weeks on the medical service of Professor Longcope (Ward Osler 5) for special metabolic and other studies under the direction of Dr. G. A. Harrop. On December 31, 1932, he entered Ward Osler 6 because of an infection contracted two weeks earlier, followed by high fever, pain in the chest, right side in back,

*Clinic to the Senior Students of the Johns Hopkins Medical School, January 12, 1933.

sore throat and an erythematous skin eruption. (Supervision by Dr. J. T. King, Jr., and Drs. Winkenwerder and Hardy.)

The members of the medical staff have been deeply interested in him because of his failure to grow normally after the sixth year and efforts have been made to ascertain the causes of his dwarfism.

Family History. His parents and nine living sibs are all of normal size. One sister has been nervous and has had occasional enuresis. The mother suffers from migraine. One cousin on the father's side is said to be 6 ft. 6 in. in height.

Figure 1. Patient L. H. beside a well-developed adult of same age.

Personal History. At birth there was fracture of both hips. He had measles at four and mumps at twelve. Throughout his life he has had recurring attacks of fronto-temporal headaches accompanied by dizziness, transient diplopia and vomiting, the attacks occurring recently at intervals of six weeks. The patient reports also frequent epistaxis, mild constipation, weakness of the left knee, rheumatic pains in the knees in wet weather, and loss of some 17 pounds in weight during the past seven years.

Development seemed to be normal until about the age of 6, when he ceased to grow at the usual rate, and after the age of 14 there was no increase in height. There was also failure of normal sexual development (both physical and psychic). He has been troubled by nocturia (urinating from one to three times each night) and by enuresis (about once a week) throughout his life.

When seen in the medical out-patient department in April, 1932, his height was about 55 inches (about 139.7 cm.), his weight 77¾ pounds (dressed), thus presenting an interesting picture of dwarfism. X-ray studies at that time showed

a rather small circular sella about the size of that of a child of 12. In roentgenograms, the epiphyses of the right shoulder, elbow and knee were found to be ununited. Examination of the eyes revealed no marked disturbances of vision or of the visual fields, and the eye grounds looked normal. His basal metabolic rate was minus 17. During the summer he was given courses of thyroid substance (32 mgm. twice daily). On entrance to the metabolism ward in October, he was subjected to a general study with especial reference to the causes of the dwarfism and to the endocrinopathy.

Physical Examination. The positive findings (in summary) included: Temperature, 99.2°; pulse rate, 116; respiratory rate, 24; blood pressure 80 to 90 systolic, 40 to 60 diastolic; weight, 29.7 kilograms; height, 139.7 cm. (55 in.); marked dwarfism and low blood pressure; face wrinkled; aspect of middle age; skin of body soft and thin like that of a child; slightly enlarged breasts; marked hypotrichosis, with absence of beard, axillary hirci and crines pubis, but with an abundance of hair on the scalp.

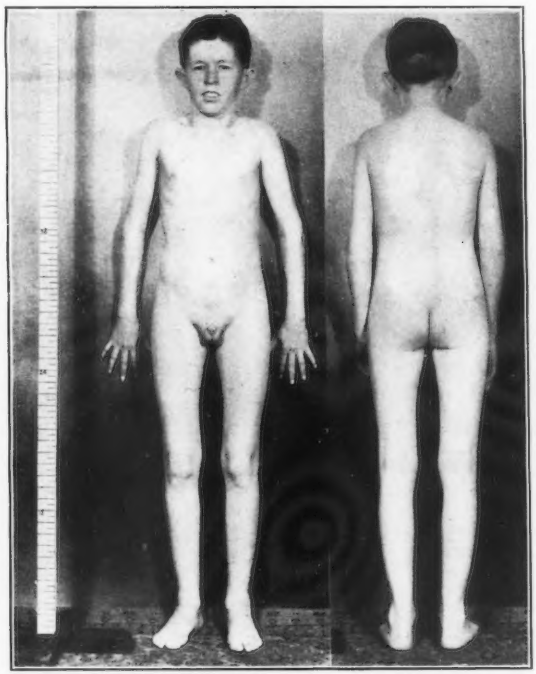

Figure 2. Patient L. H.

There was slight pallor of the mucous membranes. There was a scar on the right side of the face. The face and upper chest and shoulders were freckled. The teeth were carious and the tonsils were large. There was slight enlargement of cervical and axillary lymph glands. The lower pole of the right kidney was palpable. The genitalia were infantile with small testicles and prostate; phimosis was present. The voice was high pitched. Chvostek's sign was elicited on both sides; Trousseau's sign could not be obtained.

Laboratory Tests (on admission). Blood: The R.B.C. count was 3,890,000; hemoglobin, 88 per cent; W.B.C., 5,970. The differential count was essentially normal.

The urine was acid, contained no albumin nor sugar, occasional W.B.C., and the specific gravity was 1022.

The blood Wassermann reaction was found to be negative and the result of the flocculation test was negative.

The stool was normal.

Blood chemistry findings were: N.P.N., 30 mgm./100 cc.; Sugar, 87 mgm. per cent; Calcium, 10.4 mgm. per cent; Phosphorus, 4.7 mgm. per cent. The *basal metabolic rate* was minus 22 to minus 24 on October 11.

The *glucose tolerance test* revealed a high carbohydrate tolerance, such as is often met with in cases of myxedema.

Renal function tests yielded results within normal limits.

The *stomach contents*, fasting, showed no free hydrochloric acid and total acidity, 5. One-half hour after 100 cc. of 7 per cent alcohol, free hydrochloric acid 19, total acidity 28.

Dental Examination showed several cavities and marked alveoloclasia. One tooth was periapically infected (to be extracted). The pulp chambers of the central incisors were the size of those of an 8-year-old child.

Figure 3. Patient L. H.

Psychiatric Report (Dr. Muncie): The mental age was 17 years, 4 months; fairly well adjusted to dwarfism. Social life was apparently adequate. Sex life was undeveloped physically or mentally.

Diagnosis. 1. *Dwarfism* (height, 139.7 cm., and weight, 29.7 kg. at age of 24), with history of retardation of growth in height at age of 6 and cessation at age of 14.

2. *Endocrinopathy*, with premature arrest of growth in height and of sexual development, but with fair development of intelligence and of social nature; ununited epiphyses, infantile genitalia, failure of development of secondary sex characters (high pitched voice; absence of barba, hirci, and crines; lack of sexual libido and potentia), low blood pressure, retardation of basal metabolic rate (minus 22 to minus 24), increased glucose tolerance, bilaterally positive Chvostek sign, and progeric facies.

3. *Oral sepsis* (one tooth to be extracted because of periapical infection; dental caries with multiple cavities).

4. *Hypertrophic tonsils* with slight regional lymph gland enlargement, and with slight arthritis (knees).

5. *Secondary anaemia* (r.b.c. 3,890,000; Hb. 88 per cent).

6. *Gastric subacidity* and *slight constipation.*

7. *Migraine* (with history of migraine in mother).

Course in the Hospital. The infected tooth was extracted and circumcision was performed in the hope that the enuresis might be overcome. The condition of the blood improved during the time the patient was in the hospital. Thyroid extract was administered beginning with a dosage of 96 mgm. per day and increasing to 224 mgm. per day; as slight tachycardia developed the dosage was reduced to 160 mgm. per day—64 mgm. at 8 A.M., 32 mgm. at noon and 64 mgm. at 4 P.M. He left the metabolism ward on October 29, 1932.

On November 26 he reported at the Endocrine Clinic of the out-patient department, where Dr. J. E. Howard made the note that he had been on 2½ grains (160 mgm.) of thyroid daily for six weeks. His weight and height had remained stationary. Treatment with subcutaneous injections twice weekly of 1 ccm. of antuitrin G (P. D. & Co.) was then begun.

In mid December he developed sore throat with cough and a temperature of 104° and remained in bed for five days. On the day after Christmas he felt severe pain in his chest and back and three days later erythematous blotches (some of them 4-6 cm. in diameter) appeared on the skin of his extremities, the tonsils were enlarged and reddened, and the pharynx was injected. There was a slight secondary anaemia (r.b.c. 4,450,000, Hb. 73 per cent) and a marked polymorphonuclear leucocytosis (w.b.c. 24,080, PMN 81 per cent). Roentgenogram examination of the chest revealed no consolidation of the lung. A systolic murmur was temporarily audible over the base of the heart but it disappeared later. Though there was no pain or swelling of the joints, the possibility of an acute rheumatic fever was kept in mind. On January 4 the leucocyte count had fallen to 16,200 and on the following day to 14,200. He improved steadily, the leucocytosis decreased and he returned to his home a few days later.

DISCUSSION OF THE CASE

Aside from the migraine (inherited directly from the mother) and the focal infections (peridental and tonsillar causing slight lymph gland enlargement, slight arthritis and secondary anaemia of moderate grade) the interest in this case centers in the *dwarfism* and the evidences of *multiglandular endocrinopathy.*

It is customary to distinguish between disproportionate dwarfs (achondroplasic, rachitic, cretinoid, etc.) and proportionate dwarfs (primordial, infantile). This patient obviously falls in the group of "infantile proportionate dwarfs" for, in the first place, the boy is not achondroplasic, rachitic or cretinoid, and, in the second place, primordial proportionate dwarfism (nanosomia primordialis) is ruled out, since the condition is not familial (parents and nine sibs are of normal size), he developed normally as a child until about the sixth year, when growth in height became slowed and later arrested, genital function never developed, and the epiphyses have remained open. In primordial dwarfism (Tom Thumb type), the person is, aside from his diminutive size, apparently perfectly normal, both physically and mentally, or, as is often said, he is "a normal person viewed through the large end of an opera glass." He is small at birth, his father and brothers are usually small (a race of pygmies), the sex organs and functions develop normally, the epiphyses close, and there are no marked evidences of disturbances in endocrine domains.

That there have been marked endocrine anomalies in the case here reported is certain. On analysis, these anomalies are found to be referable to hypophyseal, thyroid, gonadal, and (possibly also) parathyroid domains.

The parathyroid disturbance (if any) must be very slight; the Chvostek sign is bilaterally positive but there has been no other suggestion of tetany.

The thyroid disturbance is somewhat more marked, as the basal metabolic rate is retarded (minus 24), and the glucose tolerance is slightly increased, but there are no other signs of hypothyroidism, the skin is not thickened and the development of intelligence has been approximately normal.

The gonadal disturbance is of high grade, as the testes are small, the secondary sex characters have not developed, and the epiphyseal junctions have remained unclosed.

The hypophyseal disturbance is the most profound of all the endocrine disturbances, for, despite the failure of epiphyseal closure, growth became greatly slowed at the age of six and practically ceased at the age of fourteen, indicating either deficiency of the growth hormone of Evans, or failure of the vegetative apparatus through which it acts. Though the sella turcica is small in roentgenograms, I do not lay much stress upon this, for clinical-pathological studies have shown that it is very unsafe to draw conclusions regarding the size and functions of the pituitary gland merely from small size of the sella. It is very probable, in my opinion, that the failure of the sex organs and of the secondary sex characters to develop in the patient has been due, in turn, either to deficiency of the sex-hormones of the hypophysis (prolans) or to failure of these hormones to act through the vegetative centers in the hypothalamus upon which under normal conditions they are believed to impinge. Even the depressed basal metabolic rate may be due to deficiency of the thyroid-stimulating hormone that the hypophysis normally manufactures. If these views be correct, the infantile nanosomia with which we have here to deal must be regarded as being predominantly hypophyseal in origin. Whether the arterial hypotension (systolic blood pressure 80) may be in part dependent upon deficiency of the blood pressure raising hormone of the hypophysis (vasopressin or tonephin) is a question that might also reasonably be asked. That the anti-diuretic principle manufactured by the hypophysis has not been lacking seems probable, since there has been no evidence of diabetes insipidus; there has been no polyuria and the kidneys have been able to secrete a concentrated urine of high specific gravity (1022).

If the dwarfism be of hypophyseal origin, as I believe, it must be due to involvement of the anterior lobe (adenohypophysis) with reduction of its growth promoting and sex promoting functions, or to injury to the hypothalamic vegetative nerve-centers through which the hormones produced by the adenohypophysis exert their action. The fairly normal intelligence of the patient, the absence of obesity (such as is seen in Fröhlich's syndrome of dystrophia adiposogenitalis), the absence of disturbances suggestive of involvement of the optic chiasm or the optic nerves, and the relative normal appearance of the roentgenogram of the skull

are points that militate against the idea that any extensive destructive lesion of the base of the interbrain exists.

What then can be the pathogenesis of the hypohypophysism that we assume is responsible for the clinical manifestations in this patient? I have studied the bibliography of the subject carefully with particular reference to cases of hypophyseal dwarfism that have come to autopsy after thorough study of the symptoms during life. There are not many on record, but the cases have been collected by Erdheim and especially, recently (1932), by Berblinger. In Cushing's collected papers on the "Pituitary Body, Hypothalamus and Parasympathetic Nervous System," just published, there are also recorded many data that are helpful in the formation of judgment.

At least four cases of hypophyseal dwarfism have been thoroughly studied both clinically and at autopsy.

In Erdheim's case, a man of 38, 142 cm. in height, the testes were hypoplastic, the prostate, seminal vesicles and penis were infantile, there was absence of beard and of axillary and pubic hair, and the epiphyses were ununited. At autopsy there was found a mixed tumor that contained cysts and had become calcified and partially ossified. This tumor, which had originated in the cranio-pharyngeal duct, was relatively benign and had evidently been present for a long time, with the result that only traces of the anterior lobe of the hypophysis remained.

In Altmann's case, a girl of 17, 129 cm. in height, the epiphyses had also remained ununited and the anterior lobe at autopsy was found to have undergone extreme atrophy because of a craniopharyngeal duct tumor.

In Priesel's case, a man, 132 cm. in height, had begun to be inhibited in growth at the age of 15, but lived to the age of 91. He remained through life a proportionate dwarf with small testicles, though the epiphyses all became united, and he was of good intelligence. At autopsy, it was found that the adenohypophysis and the neurohypophysis had never come into apposition inasmuch as the latter lay behind the optic chiasm and the infundibulum (dystopia of the neurohypophysis). The adenohypophysis in the sella was rudimentary having been almost entirely replaced by a cyst that communicated with a widened portion of a persistent craniopharyngeal duct.

In Berblinger's case, a man who died at 22, there had been marked inhibition of growth. At the age of 15, he was only 135 cm. in height and weighed 28.5 kg., the average normal height at that age being 153 cm. and the average normal weight 43.9 kg. Between his fifteenth and his twenty-second year he increased only 9 cm. in height and 6.5 kg. in weight. He had all the physical characteristics of pituitary dwarfism and was of good intelligence. But there were also signs of intracranial neoplasm (headaches, vomiting, vertiginous attacks, diplopia, left abducens paralysis and bilateral choked disc). In roentgenograms of the skull, the entrance

to the sella was widened and, above it, some shadows due to calcification could be seen. A probable diagnosis was made *intra vitam* of "pituitary dwarfism due to extrasellar neoplasm in the region of the junction of the infundibulum with the neurohypophysis." The patient died of pulmonary and intestinal tuberculosis and at autopsy, an extra-sellar craniopharyngeal duct tumor (partly solid, partly cystic) was found in the region of the stalk of the hypophysis displacing the floor of the third ventricle upward, having infiltrated and destroyed a portion of this floor. The stalk of the hypophysis was replaced by the growth and the pars tuberalis of the adenohypophysis was destroyed. The main mass of the glandular portion of the hypophysis itself was flattened and, on histological examination of the anterior lobe, chromophobe cells outnumbered the chromophile cells. The injury to the anterior lobe was not sufficient to render it non-functional and Berblinger believes that the dwarfism was due to interruption of the connection of the adenohypophysis (by way of the pars tuberalis) with the interbrain.

Cushing, in his Lister lecture (1930) has described cases of pituitary dwarfism that were shown at operation to be associated with cysts or tumors originating in Rathke's pocket (craniopharyngeal duct).

In our patient the clinical phenomena would seem to favor, therefore, the idea of the existence of a neoplasm or of a cyst having its origin in the ductus craniopharyngeus and causing either injury to the adenohypophysis itself (anterior lobe) with diminution of its function, or breaking its connection with the vegetative centers in the interbrain. If we are dealing with a neoplasm or cyst, it must be of benign type for the symptoms of hypophyseal hypofunction have already existed for 18 years. It is not probable that roentgenotherapy or organotherapy would exert much beneficial effect, though either or both might well be tried. Roussy and his colleagues in Paris report a case in which the symptoms were ameliorated by x-ray treatment. It would be wise, in our case, I think, to give, over a long period, extracts of the whole adenohypophysis of animals intramuscularly in the hope of benefit.

COMMENTS UPON THE FUNCTIONS OF THE DIFFERENT TYPES OF CELLS IN THE ADENOHYPOPHYSIS

For a fuller discussion of the functional significance of the different types of cells observable in the glandular part of the hypophysis, the publications of H. Cushing and of W. Berblinger should be consulted. I can give here only a brief summary of the ideas that seem at present to be dominant.*

As is now well known, the main portion of the adenohypophysis contains three main types of epithelial cells in addition to its connective tissue and blood vessels: (1) "chief cells" or chromophobe cells, (2)

*Since this report was written an important paper has appeared upon the different hormones of the anterior lobe. c.f. Evans, H. M.: Present position of our knowledge of anterior pituitary function, J. A. M. A. **101:** 425-432. 1933.

eosinophile cells (sometimes called oxyphile or acidophile cells), and (3) haematoxylinophile cells (sometimes called basophile cells—a somewhat objectionable term since, with Mallory's stain, the so-called basophile granules stain with acid aniline blue). The eosinophile and the basophile cells are together spoken of as the chromophile cells of the hypophysis.

Many believe that particular functions are subserved by each of these three types of epithelial cells, even though it is thought by some that the chromophobe cells are the relatively undifferentiated mother cells of the two varieties of chromophile cells. The general opinion is that the eosinophile cells manufacture the growth hormone of Evans and that the basophile cells manufacture the sex hormones or prolans, prolan A being the hormone that stimulates the follicles of the ovary, prolan B being the luteinizing hormone. (Parenthetically, Novak has stopped a certain type of functional uterine bleeding by the administration of prolan B which through its action on the ovary increases the production of progestine, which in turn favorably influences the endometrium.)

Again, in the tongue-like process of the glandular part of the hypophysis that is projected into the tissue of the vascular membrane of the infundibulum, there are cells similar to chromophobe cells (but according to Benda not identical with them) and cells similar to the basophile cells (but perhaps differing from them and called by Benda "pseudobasophile" cells). It is thought by some that the cells of this tongue-like process (pars tuberalis) of the adenohypophysis manufacture the anti-diuretic substance (in pituitrin) and possibly also vasopressin (tonephin) and oxytocin (orasthin).

In human beings it does not seem possible to separate a pars intermedia from the rest of the glandular hypophysis, though in certain animals this is possible; in them it is believed to manufacture vasopressin, oxytocin, the anti-diuretic hormone, and intermedin (the substance that affects chromatophores in frogs and fishes). In man the adenohypophysis combines the functionally different secreting parts of animals, just as the human pancreas combines the islands of Langerhans (that make insulin) with the main portion of the gland to make a single organ though in lower forms the islands are separate.

The growth hormone made by the eosinophile cells appears to go over into the blood directly, whereas the sex hormones and the anti-diuretic substance, though manufactured in the adenohypophysis, do not go directly into the blood but pass, at least in part, through the posterior lobe and the pedicle (perhaps undergoing some change during passage) into the interbrain.

In pregnancy, the adenohypophysis becomes enlarged and there is hypertrophy and hyperplasia of the chief (chromophobe) cells. A somewhat similar change in the chief cells occurs on intraperitoneal injection of placental extracts or of peptones.

In castrated animals (as well as in castrated human beings) there is often an increase of the eosinophile cells of the hypophysis, possibly because of removal of a restraining effect of the gonads.

In hypothyroid states, hypertrophy and hyperplasia of the chief cells occur, as MacCallum and Fabyan showed some years ago, whereas in hyperthyroid states, the basophile cells degenerate, the eosinophile cells are sometimes decreased in number and there is no increase or hypertrophy of the chief cells.

In deficiency of the suprarenal glands (Addison's disease) there is a marked decrease in the number of basophile cells.

In some chronic renal diseases with arterial hypertension, an increase of the basophile cells has been observed.

Turning to the hypophyseal diseases themselves, great progress has been made in the study of the pathogenesis of acromegaly and certain forms of gigantism, of hypophyseal dystrophia adiposogenitalis, of pituitary dwarfism, of Simmonds' cachexia, and of the condition known as Cushing's syndrome. Thus, acromegaly and some cases of gigantism seem to be due to hypophyseal adenoma composed of eosinophile cells (and when associated with genital dystrophy to injury of basophile cells); dystrophia adiposogenitalis (like diabetes insipidus) appears most often to be due to tumors or other lesions that injure both the hypophysis and the interbrain; pituitary dwarfism is most often due to cysts or tumors arising from rests of the ductus craniopharyngeus that either slowly injure the total function of the adenohypophysis itself or block the passage of its growth and sex increta from the hypophysis to the vegetative centers in the hypophysis (Gilford's ateleiosis is probably merely a mild form of pituitary dwarfism); Simmonds' hypophyseal cachexia depends upon rapid loss of total anterior lobe function either from destruction of its cells or from failure of its increta to reach the vegetative nerve-centers; and Cushing's syndrome (striped abdomen, high blood pressure, hypergenitalism, hypertrichosis, etc.) is referable to basophile adenoma of the anterior lobe.

Though we may still be only at the beginning of knowledge regarding the functions of the hypophysis cerebri in normal and in pathological states, it must be admitted that the progress made since the opening of the new century has been most gratifying and is full of promise for an ever better understanding of the hypophyseopathies.

SUMMARY

A boy of 24 was studied because of underdevelopment after the sixth year of life, severe headaches, frequent urination and weakness of the left knee. The father was 6 ft. 6 in. in height and the mother suffered from migraine.

Examination showed: Height of 139 cm., and weight, 29.7 kg.; pulse rate, 116; low blood pressure; marked dwarfism with ununited epiphyses, hypotrichosis, failure of secondary sex characters to develop, and basal

metabolic rate minus 22; periapical dental infection; chronic tonsillitis; secondary anaemia; slight arthritis.

He was regarded as an infantile proportionate dwarf dependent upon either a neoplasm or cyst originating in residues of the ductus craniopharyngeus and causing injury to the adenohypophysis (or to its connections with the interbrain) with resulting hypohypophysism, hypogenitalism and hypothyroidism.

Similar cases reported in the literature are cited.

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PSYCHOSES, PSYCHONEUROSES, AND ENDOCRINE DYSFUNCTION*

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This report deals with the results of studies carried out on a consecutive series of patients referred for diagnosis and who presented some form of mental disease as a feature in the final summary of the case. The Evans Memorial, under ordinary conditions, is not organized to furnish custodial care, and so a primary reference for mental disease was limited to the few individuals to whom adequate nursing supervision did not entail an expense which was prohibitive. The great majority of the patients comprising the group had given evidence of physical abnormalities calling for diagnostic resolution. The mental status either was established during the course of the study or had been previously recognized and the patient referred during its incipiency or in a period of temporary quiescence.

The general method of study has been frequently reported (1), and need not be elaborated here. In addition to the usual procedures applied routinely, careful psychiatric studies were made by one of us (H.M.P.) of the majority of the patients in the group. Further, with but few exceptions, additional reports from one or more psychiatrists, outside the staff of the institution, who had examined the patient, constituted a part of the available data for each individual.

It is generally recognized that personality changes are frequently observed in an individual coincidently with the onset and progress of some one of the several endocrinopathies. From this, it has seemed to us interesting and potentially informative to analyze this group of patients, each of whom exhibited serious departures from the normal in their several personality patterns, from the standpoint of associated deviations from normal physical function. At the start we wish to disclaim any attempt to establish a causal-resultant relationship between the physiological and psychological associations which this study discloses. The patients in the mental group were but a segregated part of a larger series of individuals, sixteen times as numerous, all presenting the same physical etiologies but without demonstrating the mental element. In other words, but one in sixteen of a series of four thousand patients with a selected group of physical backgrounds gave recognizable evidence of mental abnormality. Such a fact denies any simple causal relationship but equally allows trends

*Presented by Title at the Seventeenth Annual Meeting of the Association for the Study of Internal Secretions, Milwaukee, June 13, 1933.

of association to assume some significance. What these are will be discussed in the body of the text; the present credo serves only to define a position for the benefit of the unbiased reader.

Turning to the material deriving from analysis, the composition of the study group can be presented most compactly in tabular form.

TABLE I
GENERAL DATA

Sex	Psychosis	Psychoneurosis	Total
Male	30	23	53
Female	80	117	197
Total	110	140	250

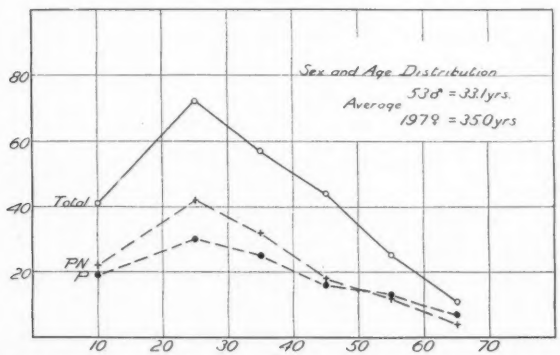
The psychotics and psychoneurotics are not quite equally represented, the latter showing a modest preponderance. This might be anticipated from the limitations attending the reception of patients, as noted above. Women outnumber men nearly four to one, a proportion that is definitely at variance with the usual distribution of mental disease in the community, where the sexes are usually approximately equally represented.

This possibly derives from the somewhat selective character of the whole series from which the mental group is drawn. Representative figures from the population of this institution show roughly 75 per cent females in the endocrine and 60 per cent in the complementary series (some 40 per cent of the whole) of individuals without involvement of the ductless glands.

The age distribution is also a basic datum and the relative partition among the several decades is presented in graphic form.

The distribution in the two groups is substantially the same, the minor differences being apparent in the graph. Likewise the average age of the two sexes shows only an unimportant difference.

GRAPH I



Age distribution by decades in psychotic and psychoneurotic series.

As was noted above, the mental group is a small selected portion of a much larger general diagnostic series, the majority of the patients in which gave putative evidence of some endocrine disorder as the usual reason for their initial reference. Study confirmed the initial suggestion of glandular involvement in but 60 per cent, as already stated. The relative distribution of the major categories in the two series is not without significance as lacks of agreement may be interpreted in terms of tendencies of association.

TABLE II
ENDOCRINE INCIDENCE IN TOTAL AND MENTAL SERIES

Group	Series	
	Mental	Total
Pituitary	40.8%	30.1%
Thyroid	12.4%	14.8%
Gonad (Ovary)	21.6%	12.8%
Other Endocrinopathy	1.2%	2.1%
Non-Endocrine	24.0%	40.2%
Number	250	4000

Obviously there are several suggestive differences in distribution between the two series. The larger relative representation of pituitary and ovarian cases in the mental series is of a sufficient magnitude to be significant. Further, the association of these two glands in this connection cannot be regarded as wholly fortuitous when one considers their close interrelationship. While the mental group is a small one, past experience has shown that the changes in scatter from year to year in this institution are of insignificant proportions. It seems warrantable to suggest that the data of Table II define a possible trend of association between mental disease and endocrine dysfunction. Equally, it is significant that in a series, weighted as is the present group toward a high endocrine component, one in every four of the patients presents clear-cut mental disorder without evidence of incretory aberration.

The mental group automatically divides into two major divisions and the relative incidence of the several primary physical associations in each next comes under scrutiny.

TABLE III
PRIMARY ETIOLOGY

Group	Psychosis	Psychoneurosis	Total
Endocrine:			
Pituitary	55	47	102
Thyroid	17	14	31
Ovary	12	42	54
Pluriglandular (Thyroid and Ovary)	0	3	3
Totals	84	106	190
Non-Endocrine:			
Lesions of Central Nervous System	12	10	22
Miscellaneous	14	24	38
Totals	26	34	60

The ratio of three to one between endocrine and non-endocrine obtains equally in both of the mental series. Two-thirds of the endocrine psychotics or exactly one-half of the total psychotic group were diagnosed as having a pituitary involvement. The ovary, on the other hand, shows a high incidence of association with the psychoneuroses—a ratio of 3.5 to 1 with the psychotic fraction—and this is augmented modestly by the addition of the three so-called pluriglandular cases, all of which occurred in castrates with an associated thyroid failure. Some of the group with neural disorders, from the nature of the lesion, might be assumed to exhibit a secondary pituitary element. None of them gave objective evidence, however, for the warrant of such an assumption, and as they are fairly equally divided between the two groups, their inclusion would produce changes only in degree without influencing the conclusion. For convenience sake, the basic relationships in the foregoing table may be summarized in Table III-a.

TABLE III-a

PROPORTIONS OF PSYCHOSIS AND PSYCHONEUROSIS IN ENDOCRINE AND NON-ENDOCRINE GROUPS

Group	Psychosis	Psychoneurosis	Total
Endocrine	34%	42%	76%
Non-Endocrine	10%	14%	24%
Total	44%	56%	

The slightly greater frequency of endocrine-psychosis association is more clearly expressed by this percentile presentation.

The group of the psychoses offers a peculiar interest both from the gravity of the mental condition and from the prevalence of manic depressive insanity and dementia praecox in the community.

Adopting these two terms to designate broadly two large classes of psychotic aberration (roughly speaking, some 40 per cent of all first admissions to state hospitals) and combining the remainder of the cases in a third miscellaneous group, the distribution of the members of the series is presented in Table IV.

Turning first to the patients with endocrine disorders, it is evident that five-sixths of those with dementia praecox have an associated pituitary dysfunction. Further, this constitutes over half of the total pituitary series. The association of manic depressive psychosis with pituitary disorders is but slightly more than one-half as frequent as with the praecox patients. The remaining pituitary cases, listed in the third group, all presented psychotic states associated with the menopause. With due consideration of the part played by the pituitary in the regulation of certain of the sexual functions, much of our knowledge of which results from the illuminating investigations of the past few years, there is perhaps an especial interest in this latter trend of association. Continued studies on a

TABLE IV

ANALYSES OF PSYCHOSES
ENDOCRINE GROUP

Group	Manic Depressive	Dementia Praecox	Miscellaneous Psychoses	Total
Endocrine:				
Pituitary	18	30	7*	55
Thyroid	9	6	2	17
Gonad	12	0	0	12
Total	39	36	9	84
Non-Endocrine:				
Lesions of Central Nervous System	1	2	9§	12
Miscellaneous	7	3	4	14
Total	8	5	13	26

*Menopausal.
§Paretic, Epileptic, Alcoholic, Senile.

larger series, however, will be necessary to confirm or deny the implications of this observation.

The thyroid cases show a rather non-distinctive distribution, although there seems to be a slight weighting to an association with the manic depressive group. The unhappy mental state of the victim of severe thyroid failure suggests in its features certain parts of the pattern that defines the depressed phase of the psychosis. The ovarian series also show clear-cut association with this class of mental disease, and in the present study group offer no exception. This is probably fortuitous and due to the small number of cases, as with the type of ovarian failure which seems to succeed and be the result of an earlier pituitary aberration* later normalizing spontaneously, one would anticipate possible association with other forms of mental derangement.

In the non-endocrine fraction, nearly one-half of the cases are associated with recognized disorders of the central nervous system; the remainder show an uninformative scatter of associations with a variety of non-glandular derangements. Adopting the convention already followed with Table III, the relative incidences may be summarized in tabular form.

TABLE IV-a

SUMMARY OF PSYCHOSES

Group	Manic Depressive	Dementia Praecox	Miscellaneous Psychoses	Total
Endocrine	35%	33%	8%	76%
Non-Endocrine	7%	5%	12%	24%
Total	42%	38%	20%	100%

In manic depressive psychosis and dementia praecox, there is a dominant incidence of endocrine association with, however, an appreciable number of cases without incretory disease. In the miscellaneous group,

*The description and discussion of this syndrome, if such it prove to be, will be given in the near future. Data are now available to warrant belief in its probable existence.

the distribution is reversed and the endocrine moiety largely confined to the psychoses of the climacteric with a definite pituitary association.

DISCUSSION

Limiting consideration for the moment to the small series with mental disorders, a seemingly warrantable inference to be drawn is that there exists a very high incidence of association between the mental disorders and disorders of the ductless glands. But even in this highly selective group, an appreciable number—one-fourth—show the same types of mental disorder and demonstrate freedom from objective evidences of endocrinopathy. Further, this small group is drawn from one many times as large and composed of people presenting the same physiological backgrounds as do those of the study group. For example, in the larger series there are 1204 individuals with some type of pituitary disorder. Of this number 102 or less than 10 per cent show a complicating abnormal mental status. Recorded in concrete terms, the several associations are as follows:

TABLE V

RELATIVE INCIDENCE OF MENTAL CASES IN TOTAL SERIES

Group	Total	Mental	Per Cent
Pituitary	1204	102	8.5
Thyroid	592	31	5.2
Ovary	512	54	10.5
Total Endocrine			8.1
Not Endocrine	1608	60	3.7

The small number of cases with other endocrinopathies are omitted as they are too few to be significant. This more drastic analytical approach confirms the first impression, as stated at the beginning of the discussion. Mental disorders are more than twice as frequent in the endocrine as in the non-endocrine series in spite of the fact that in this latter group there is a relatively large number of patients with conditions conceded to be productive of mental disorder. The case for selective association of psychoses and psychoneuroses with endocrine disorders would seem to be reasonably supported for a group all of whom show significant and tangible departures from a state of normal physical health. For it is to be remembered that these were all sick people, their ill health being the basis for the diagnostic study.

Turning now to a closer analysis of the endocrine associations, the following further inferences are consistent with the data. There is apparently a selective association of dementia praecox with pituitary dysfunction as practically three-fourths of the patients with this condition exhibit evidence of disturbed hypophyseal function. The converse is not true as nearly one-half of the pituitary cases are found in patients with other forms of psychosis.

Thyroid failure in this relation to patients with and without mental disease shows the least significant trend of association, yet even here the relative incidence exceeds appreciably the figures of the non-endocrine group. If there be a trend in the psychotic fraction, it is for association with manic depressive insanity.

Ovarian failure is much more frequently recorded in the psychoneurotic than in the psychotic series; when it appears in the latter, the association is solely with the manic depressive type of insanity.

Now if these points are conceded—and on the basis of objective data they would seem to possess a reasonable warrant—the question next arises of how they shall be interpreted in terms of the etiology of mental disease, if indeed such interpretation be possible.

One of us (A.W.R.) has made a similar analysis of a group of children presenting behavior problems (2), so-called, of varying degrees of gravity. As in the present group, a high incidence of associated endocrinopathy was remarked and likewise it was noted that the number of children both with endocrine disorders and without recognized behavior problems far exceeded in number those in the study group.

That the endocrine glands are among though not the only potent regulators of growth and development, will be conceded by all. Many of their effects are mediated through and by that vastly complex series of interrelated mechanisms which we conveniently group under the title of metabolism.

In the child with the behavior problem, in the patient with mental disease, there is no inevitability in an association with endocrine malfunction. Even more, as these figures attest, is there an equal or even greater lack of unvarying sequence of mental disease following or occurring with functional disorders of the ductless glands. On the other hand, the high degrees of correlation that have been recorded cannot be fortuitous as they certainly are not artefactual.

In other words, all of the 250 patients composing this series show marked evidence of metabolic disturbance and likewise equally marked deviations from normal mental levels. That the great majority of the larger series with like metabolic derangements fail to show equivalent mental disorders implies the presence of at least another deciding factor in the equation. That a tendency to mental disease is transmissible from generation to generation is a well documented and generally accepted belief. Such a constitutional tendency to mental disease, deriving either from heredity or from other predisposing factors of the nature or even existence of some of which we are today ignorant, could furnish a soil fertile to outside influences. These could be psychogenic or physiogenic—in some cases probably both—and here again the presence of the two components need not necessarily produce an end result of a psychosis.

In the study of human fertility we are recognizing today what may be called a fertility index for each partner. This is a quantity which is

the elaborate summation of a wide variety of favoring and opposing agencies intrinsic in, and characteristic of, the individual possessing them. Fertility of union results when the combination of these two indices of the two partners, thus constituting a "mating index," is superior to a certain critical zone or boundary. Thus fertility is usually a relative term falling between the limits of absolute sterility and absolute fertility. The partners in an infertile union will both frequently demonstrate power to reproduce when mated with other partners of a higher relative fertility.

So with the causal factors in a psychosis, one could conceive of the two necessary components, one, a constitutional tendency of diverse and varied origins, the other, the outside agent, simple or complex, psychological or physiological, one or both, and these two acting together to produce the end result of mental disease. In such a concept there is again no inevitability. All of the factors may be present but they become productive only if the summation of their several indices exceed a critical boundary.

In any case, all of the patients with mental disease showed marked metabolic disturbances; approximately three-fourths of the group had definite endocrinopathies while many of the remainder exhibited various recognized disorders known to produce mental disease as one characteristic feature of the condition.

As was noted earlier in the text, the dominant majority of these cases were referred to the institution for diagnostic study by physicians in various parts of the East. Naturally, these patients were returned to their own medical attendants for further care at the completion of the diagnostic survey. They were accompanied by a full transcript of the results of the study supplemented by the recommendations for treatment indicated by the findings. For this reason, the conduct of a controlled opotherapy was the exception rather than the rule. In some instances, the referring physician requested the institution to assume the care of the patient; in others, patients living at distances not too remote have returned from time to time at the suggestion of their medical advisors for further control studies.

Through the courtesy of the Department of Mental Diseases, it has been possible to refer a small number of cases to the Research Department of the Worcester State Hospital.*

Our own series of therapeutic studies is far too limited to warrant other than the most tentative of suggestions. Enough viable material has been accumulated, however, to permit one possible indication.

In cases having recurrent attacks of manic depressive insanity and demonstrating a definite endocrine malfunction, the controlled exhibition of the indicated glandular product has seemingly prevented recurrence for periods much in excess of the earlier quiescent intervals.

*Grateful acknowledgment is made to the former Commissioner, the late Dr. George M. Kline, to Dr. William A. Bryan, Superintendent of the Hospital, and to Dr. R. G. Hoskins, Director of the Memorial Foundation for Neuro-endocrine Research.

In a paper already presented at this meeting by one of our colleagues, Dr. Hector Mortimer, the basic thesis deals with the recognition of present and past pituitary functional derangements which have produced characteristic types of cranial dysplasias. From these and the additional factual material drawn from complete diagnostic studies, it is possible, in some measure, to reconstruct the levels and fluctuations of pituitary function during the earlier years. He has noted that the initial observations which led to his research were made on skull radiograms of patients in the Worcester State Hospital. Further, in the analysis of the skull plates drawn from a consecutive series of 3000 cases studied in the Evans Memorial he has reported a definitely larger relative incidence of psychoses and psychoneuroses in the pituitary cases with cranial dysplasia than occurs in the entire pituitary population of the institution.

For the moment, certainly, conservatism bids that we regard these several observations as the interesting associations that they certainly are. The point of real importance lies in the fact that they definitely indicate a trend, the true implication of which it remains for further investigation to resolve. One line patently before us is the therapeutic approach to psychotic individuals demonstrating characteristic patterns of cranial dysplasia.

SUMMARY

The paper presents a survey of the underlying etiology of 250 patients with psychoses or psychoneuroses drawn from a consecutive series of 4000 individuals of which they were a part. On hundred and ten were psychotic; psychoneuroses composed the larger remaining fraction. Roughly, three-fourths of the series presented some form of endocrine disorder; the remainder were equally free of demonstrable evidence of incretory involvement with lesions of the central nervous system as the principal single contributor. One hundred and two cases had an associated pituitary element, nearly equally divided between the two mental groups. There were about one-third as many thyroid cases with a like distribution, but only 12 of the 54 ovarian cases presented a psychosis, all of them being of the manic depressive type. Thirty of the pituitary cases had an associated dementia praecox in contrast to but 11 more from all other sources. The small group of thyroid patients showed no really distinctive distribution.

The authors disclaim any effort to establish any causal-resultant relationship between mental disease and disturbed endocrine function. They do regard the selective character of the associations as suggestive and warranting further and more extended study.

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OSSEOUS DEVELOPMENT AS AN INDEX OF METABOLIC SPEED

WITH SPECIAL REFERENCE TO THE MENTALLY SUBNORMAL AND EMOTIONALLY UNSTABLE CHILD*

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One interested in the endocrine field of endeavor is called upon to investigate a variety of mentally retarded or emotionally unstable children. The first problem is to separate those suffering from a disturbance which may be relieved entirely, or in part, by an intelligent therapeutic regime, from those in whom such an effort would be wasted. In the past it has been customary to depend upon casual observation as the deciding factor and many times this is sufficient. If, however, one uses bone development as an index of metabolic speed, irrespective of the other findings, he gets an entirely new viewpoint of the subject.

Proceeding in this manner, it will be discovered that all mentally defective or emotionally unstable children fall into three main groups, i.e. (1) those having normal bone development; (2) those having definitely retarded bone development, and (3) those having definitely advanced bone development. I shall limit this discussion to the first two classes; macrogenitosomia and other vague conditions producing abnormally rapid development are beyond the scope of this paper. I am of the opinion that any *metabolic disorder* in childhood, when sufficiently severe to produce mental or emotional symptoms, will be reflected in the bone development. The first group then may be excluded. There are exceptions to this in older children when the metabolic disorder (particularly hypothyroidism) is of comparatively recent occurrence. For all practical purposes, however, it is safe to say that normal bony development predicates normal metabolic speed. The second group may be divided into two main subdivisions: (A) The classic sufferers from cretinism, juvenile myxedema, or combined thyro-pituitary disorder, and (B) those presenting no definitely recognizable stigmata of an endocrinopathy. Of what significance is retarded bone development? Tissue differentiation from the beginning of the fertilized ovum until the completion of somatic development is dependent upon body metabolism. The developmental rate is therefore determined by the metabolic speed. In no other manner is the speed of metabolism represented so graphically as in osseous (particularly carpal) development.

Three factors have been considered as influencing the metabolic speed, i.e. (1) Neurogenic; (2) Dietetic, and (3) Hormonic. If neurogenic

*Read before the Seventeenth Annual Meeting of the Association for the Study of Internal Secretions, Milwaukee, June 12, 1933.

factors were significant, one would expect to find a consistent relationship between the more obvious forms of mental defectiveness and retarded bone development. As a matter of fact, those suffering from mongolism, cerebral trauma, and developmental defects of the central nervous system, rarely fall in this group. A well-balanced diet, including vitamines and mineral salts is always essential to growth, but it is questionable how important they are in actual tissue differentiation. Several years ago I had the privilege of looking over the roentgenograms of nearly a hundred cases of severe rickets, and I was surprised to find that, with few exceptions, they showed normal bone age. On the contrary, the hormonic influences

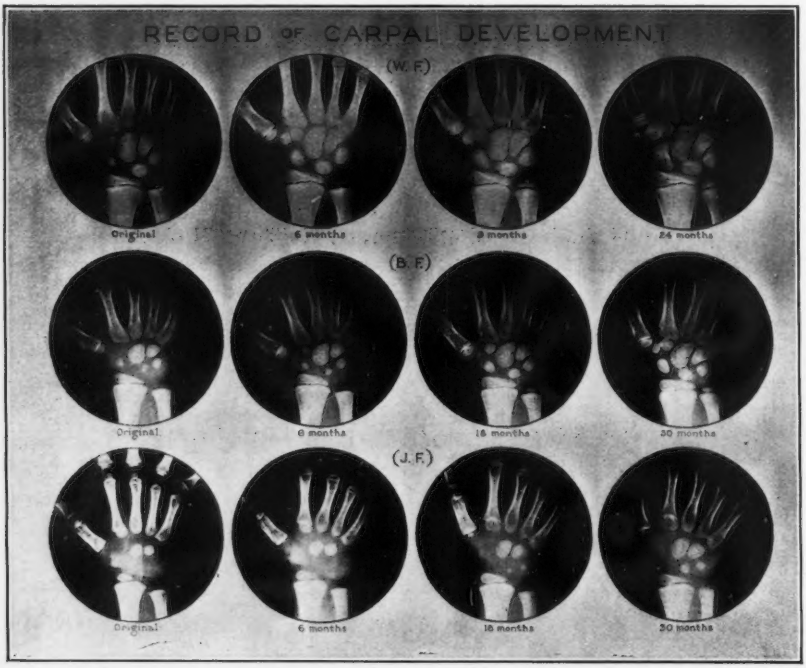

Figure 1. Record of carpal development of Patients W. F., B. F., and J. F.

on the speed of metabolism are known to be considerable. In an effort to determine the primary factor involved, we have followed the carpal development in a number of patients under treatment for the past three years.

In 1931 I presented before this society the cases of four siblings of a hypothyroid mother, no one of whom suffered from goiter, myxedema, or any other outstanding feature of the cretinic state (1). Three showed a retarded carpal development of from two to five years (Fig. 1). The oldest girl, who had a normal carpal development, was not considered in the

study. Since this time it has been my good fortune to observe W. F., B. F., and J. F., at intervals, and to keep a record of their carpal development. As pointed out in the beginning, all three have had exceptional dietary advantages since birth. During the intervening two years, six months, two of them, W. F. and B. F., have taken thyroid continuously, while J. F., owing to a series of infections with chest and cardiac complications early in the experiment, received only minute doses for a short period. It becomes necessary to revert to the original roentgenograms and again compare them with the approximate normals for the age. At the time of the first observation, W. F. had a chronological age of 10 years 6 months, and a bone age of 5 years 6 months, approximately five years retarded. B. F. had a chronological age of 7 years and a bone age of 5 years, approximately two years retarded, while J. F., youngest of the three, had a chronological age of 4 years 6 months, and a bone age of 2 years 6 months, approximately two years retarded.

Two years and six months after this observation, W. F. (Fig. 2) has a chronological age of 13 years and a bone age of 12 years 6 months, ap-

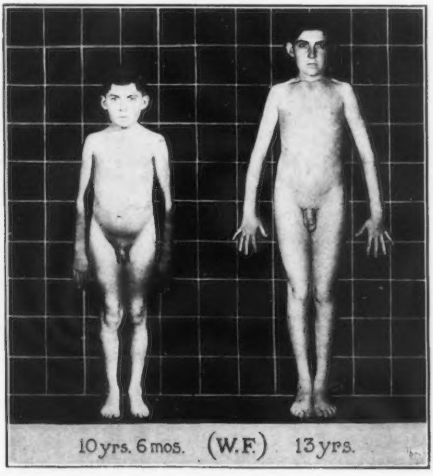

Figure 2. Patient W. F. Effect of thyroid substitution upon the soma. Both testicles were undescended at the beginning of treatment.

proximately normal. B. F. has a chronological age of 9 years 6 months and a bone age of 8 years 6 months, approximately one year retarded, while J. F., who did not have the advantage of this metabolic impetus (thyroid), in spite of large doses of Vitamin A and D over a period of a year, has a chronological age of 7 years and a bone age of 4 years, approximately three years retarded. Thus, instead of gaining, J. F. has actually lost in this relationship. It may be argued that illness prevented him from gaining, and indeed it may have a bearing on the case, but he has now been in perfect health for nearly a year without showing a gain;

besides W. F., his older brother, who was the most retarded, had very little illness of an infectious nature in childhood. Whether or not thyroid deficiency was the primary cause of the difficulties in these children, thyroid substitution seems to have completely rehabilitated two of them, while the third, without thyroid, has, if anything, slipped slowly behind. The behavioristic difficulties, so prominent in W. F. at the beginning, have been completely relieved and his somatic development has progressed to a degree at which one can say that he is a perfectly normally acting and appearing boy. These siblings were brought to me originally because of failure to gain in height. It is interesting to note that during the past two years, W. F. and B. F. have grown 2.2 inches and 0.5 inch, respectively, over the optimal increment, while J. F. fell 1.2 inches below the optimal increment.

The second study I wish to present is that of a girl, J. S., 8 years and 3 months of age. The chief complaints were mental retardation, understature, painful joints and constipation. She had been observed by numerous physicians during her lifetime. According to her mother, all agreed that the patient had an incurable form of mental defectiveness. One conscientious practitioner took considerable pains to point out why she was not a cretin, and he dwelt at length upon the hopelessness of any therapeutic regime. To my knowledge, no attempt was made to ascertain her bone age. At the age of 4 years, a diagnosis of rickets was made. She was given cod liver oil and took this continuously until we saw her four years later. This was indeed fortunate for us, if not for the child, since it afforded a comparative study of no mean value. It is true that the patient presented no classic feature of cretinism—presumably because she was not a cretin. It is also true that there was but little evidence of myxedematous change. In view of the dry, sallow skin, the stupid, heavy expression, and the slow, deliberate, almost inarticulate speech, however, anyone familiar with juvenile hypothyroidism could not help suspecting the condition at the outset. In this connection, I wish to point out my reason for using the term juvenile hypothyroidism in place of the time-honored expressions, infantile, juvenile, or childhood myxedema. Myxedema is a symptom, not a disease and, unfortunately, it is usually a late or terminal development. If physicians depend upon myxedema as the essential feature in the diagnosis of thyroid insufficiency at any period of life, then they must overlook the majority of hypothyroid sufferers. The history of this small patient, other than the things mentioned above, is uninformative. She was apparently a perfectly normal, full-term baby and was not suspected of being ill until two years of age. Her diet had been adequate and well-balanced. She could not dress herself at 8 years of age and an attempt to keep her in a kindergarten was a failure. There was no history of thyroid disease or other endocrinopathy in the family. The physical examination, October 13, 1931, revealed the following: Height, 40.8 inches.; upper measurement, 23.2 inches; lower measurement, 17.6 inches; weight, 41.0 pounds;

pulse, 92; temperature 98.6. The teeth were all deciduous, very crowded and carious. The skin was sallow in color and exceedingly dry. The hair was fine and brittle. Laboratory findings showed the blood and urine to be normal. A basal metabolic rate determination was not attempted. Roentgen examination showed four carpal centers in the wrist (approximately 4 years retarded). (Fig. 3.) The sella was normal.

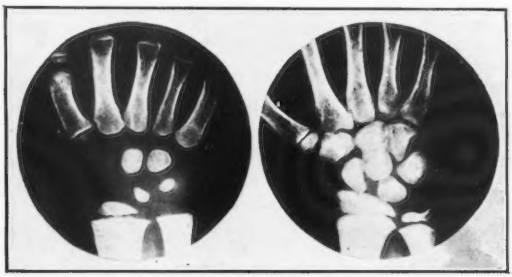

Figure 3. Patient J. S. Carpal development at the beginning of treatment compared to the approximate normal for the age (8 yrs. and 3 mos.)

On October 20, 1931, the patient was given daily 1 grain of desiccated thyroid U.S.P. at bedtime. The following week the dose was increased to 2 grains. Because the pulse ran between 116 and 120 and there was a loss in weight, the dose was again reduced to 1 grain. Wrist pictures were ordered every ten weeks. There was a remarkable improvment from the first (Fig. 4). The permanent teeth started coming in within four months. Nine months after the beginning of treatment she was in the second grade, and doing well in school.

I shall not go into all the details of the somatic change in this child within a year. Suffice it to say that she made a gain of 4.7 inches in height and 13 pounds in weight. The inequality in the upper and lower measurements gradually became less until her upper was 25.5 inches and lower 20 inches. She is now in the third grade in school. Figures 5 and 6 show the patient before treatment and a year later. The point I wish to bring out is the rapid carpal unfolding in this patient on small doses of thyroid. There was a gain of at least three years within the first year's treatment. The fact that the patient had received large doses of cod liver oil and an adequate diet for four years preceding this observation and had lost in the relationship between the bone age and chronological age is doubly informative. One other fact is pertinent. The patient had a fairly high pulse at the beginning and would not tolerate over one grain of thyroid daily. It is my belief that thyroid has both an anabolic and a catabolic effect in childhood, according to the amount given and the individual susceptibility to the hormone. Dosage is therefore of great importance in the growing ages. Within the past six months we have seen two patients, one 17, the other 29, with classic hypothyroidism. Neither had

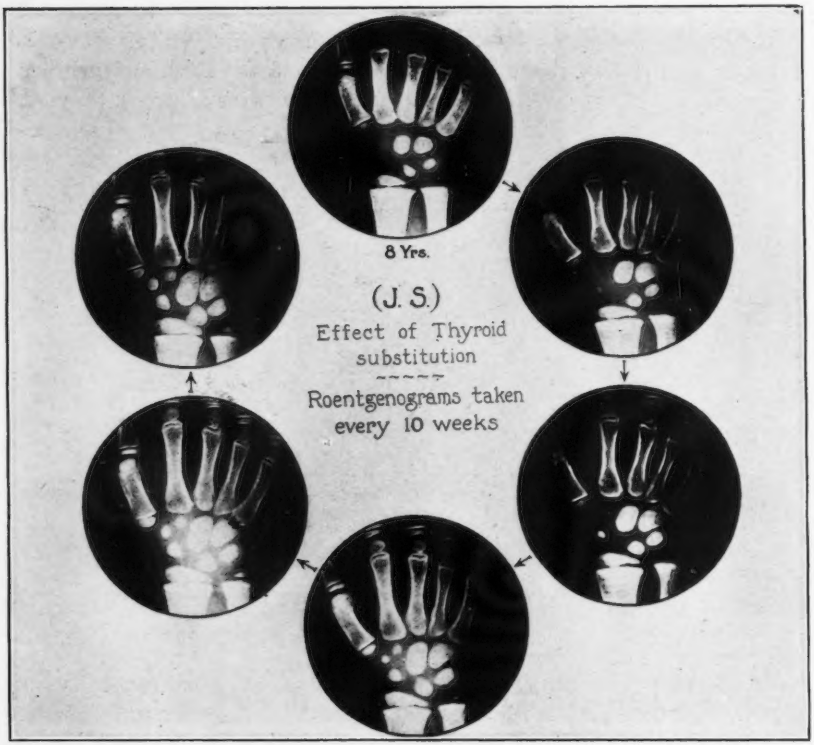

Figure 4. Patient J. S. Development of the carpal centers during the first year's treatment.

received thyroid more than a few weeks because it made them ill. Presumably, they were given large doses in the beginning, or else the symptoms, which frequently accompany rapid oxidation in myxedematous individuals, confused the attending physician. With a better understanding of the subject it would have been difficult to make such a serious mistake. The girl at 17 is still minus a pisiform, which should have appeared between 10 and 11, while the older boy did not reach adolescence until he was 24. Both of these patients are now on well-regulated doses of thyroid without untoward effect and the results have been striking. It is quite obvious, however, that the plastic periods of their lives have been allowed to pass without treatment and complete rehabilitation is a hopeless endeavor. By the same method of reasoning, every mentally defective and emotionally unstable child with sluggish somatic unfolding should be given a therapeutic chance, irrespective of the other and more casual findings. Thus, mongolism remains mongolism to the well-informed, but a mongol child, showing a definitely retarded bone age is considered as having a metabolic, as well as a neurogenic, factor to account for a part of its difficulties.

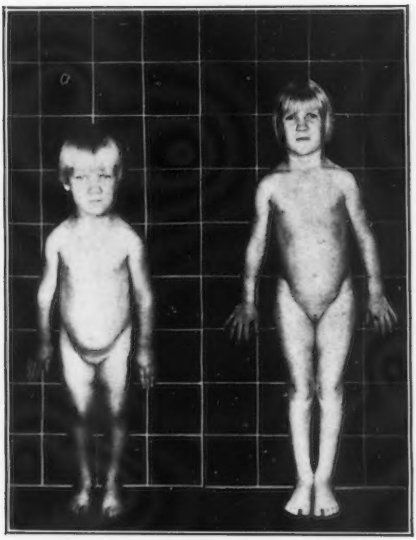

Figure 5. Patient J. S. Effect of thyroid substitution upon the soma during the first year's treatment.

Perhaps this is why some such unfortunate children improve to a degree on thyroid treatment.

Something over two years ago, in association with the Public Health Personnel of Santa Barbara County, a study was begun on 560 small chil-

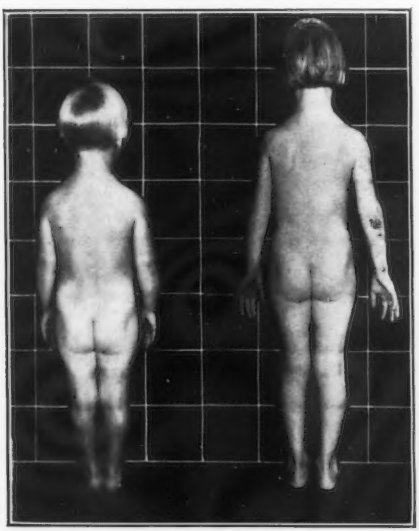

Figure 6. Patient J. S. Same as figure 5.

dren comprising the entire student body of the first four grades of certain elementary schools. Wrist pictures were secured of all. Seventy of the total, or 12.5 per cent, were found to have retarded carpal development of two years or more. The California State Psychologist then made a study of each in the retarded bone group according to the Stanford-Binet, The Arthur Performance, and The Goodenough Drawing Tests. Some of the children had low I. Q.'s, others high, while the general average fell within the limits of normal. The possibility of using bone development as an index of general intelligence was consequently again excluded. When it came time to consider in detail the history and physical examination of these children the study had to be abandoned on account of inadequate funds. Casual observation convinced me, as well as others, however, that there was a high incidence of endocrine stigmata (obesity, genital hypoplasia, statural deviations, etc.) in the group. After a lapse of two years, our attention was called again to the study in an interesting manner. At certain periods it is customary for those in authority to select a small group with abnormal behavioristic leanings (nervousness, irritability, poor social adjustment, failure in school, etc.) for study by The Child Guidance Clinic. The instructors have no knowledge of those who comprise the retarded bone group. We were therefore interested to learn that one-third of the total selected for psychiatric study fell within the retarded bone group. Since this group comprised only 12.5 per cent of the student body, originally, and several hundred children have subsequently entered the schools, the finding must be more than mere coincidence. Thus, while there appears to be no consistent relationship between bone age and mental age, the possibility of a relationship between bone age and emotional stability is suggestive. It is, perhaps, needless to state that the observation mentioned, while interesting, is not necessarily conclusive, since the study remains incomplete. The co-workers in this study were convinced of one thing, namely, that the standards of normal carpal development, including those suggested by the author (2), do not sufficiently consider the sex differences in the juvenile period.

It must be admitted that many apparently normal children have retarded bone development. The finding, per se, should never constitute a diagnosis of mental instability. The siblings, J. F., B. F., and W. F., used in this study were all very intelligent, despite the latter's introspection and poor showing in school, while J. S., of a different family, was severely retarded. The classic hypothyroid dwarf, aged 29, to whom I have referred, is a college graduate and holds a responsible position, although his mother declares that he was always "a strange child," and that he has never fitted into the normal scheme of existence. Just why the lowering of metabolic speed affects some so severely and others only slightly remains a mystery unless it can be explained by the fact that intelligence is inherently a variable. J. S. has a rather poor inheritance, while the 29-year-old dwarf is the offspring of exceptionally intelligent parents. Devoid of all

endogenous interference, the one may have been destined to an intelligence quotient of 90, the other of 130. To reduce both by 30 per cent would have been to precipitate one into a hopeless mental abyss, while theoretically the other could have struggled through school. It may be that a more careful consideration of the mentally alert child with definite retarded bone development would bring out unsuspected and far-reaching deviations from the normal. I have been impressed by the number brought in for other complaints who sleep better, eat better, eliminate better, lose their irritability and become infinitely more tractable on anabolic doses of thyroid. The danger, as I see it, is not from overenthusiasm in a consideration of this type of child, but from ultra-conservatism. There is much to gain and nothing to lose. A few months of well-regulated thyroid medication is sufficient for a thorough therapeutic test. When intelligently administered, it is quite devoid of danger.

SUMMARY AND CONCLUSIONS

One interested in the endocrine field of endeavor is called upon to investigate a variety of mentally retarded and emotionally unstable children. In the selection of those most likely to improve on an intelligent substitution regime casual observation has been the rule. When, however, one uses carpal development as an index of the metabolic status of the individual, irrespective of the other findings, he gets an entirely new viewpoint of the subject.

Three siblings and one other child with retarded carpal development have been studied clinically and roentgenologically for over two years. Abnormal behavioristic leanings were prominent in at least one of the siblings, while actual mental retardation was present in the unattached case. Two of the siblings were treated by thyroid substitution while the third was treated by the addition of high vitamin A and D to the diet. The two treated by thyroid gained rapidly in the relationship of carpal age to chronological age and were apparently rehabilitated within two years. The remaining sibling, without thyroid, lost in this relationship. The unattached subject lost consistently in the relationship of bone age to chronological age on a high calorie and cod liver oil diet over a five-year period. On thyroid substitution for a year, without cod liver oil, she apparently made a gain commensurate to a normal three-year period. The physical and mental status of this patient were markedly improved. From these and other studies of a large number of children, it is inferred that: (1) Bone age is a reliable index of the metabolic speed in childhood. (2) An abundant and well-balanced diet is not alone sufficient to maintain the normal developmental rate. (3) Addition of high vitamin A and D to the diet, even over prolonged periods, will not materially increase the metabolic speed. (4) Metabolic speed is consistently and rapidly increased by the well-regulated administration of desiccated thyroid. (5) The developmental status, as indicated by the degree of carpal unfolding,

is important in the selection of those mentally subnormal and emotionally unstable children best suited for an intelligent substitution regime.

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FURTHER STUDIES ON A GLYCERIN EXTRACT OF ADRENAL CORTEX POTENT BY MOUTH*†

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AND
R. G. HOSKINS, Ph.D., M.D.
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In a previous publication (1) preliminary observations were reported of some physiological effects resulting from the oral administration of a glycerin extract of suprarenal cortex. The investigation has been continued and a more detailed analysis of results forms the subject of the present report.

In the present investigation ten male schizophrenic patients were selected on the basis of an existing hypotension and given adrenal cortex pills§ in divided doses three times daily beginning with 9 pills, and increasing the dosage by this number each week until in six weeks they were receiving forty-five pills a day. As each pill contained extractives of ten grains of fresh cortex, the maximum dosage represented approximately an ounce of cortical substance. The medication was administered over a period of thirteen weeks and then discontinued to study the effects of withdrawal of the drug. To re-test the results and to get further light on the optimal dosage, after a rest period of seven weeks, the pills were again given to nine of the previous ten patients, this time beginning with a dosage of twelve pills, t.i.d., representing 360 grains of suprarenal cortex. As an effect upon the blood pressure as great as that first seen was not obtained in three weeks, the dosage was increased to forty-five pills daily. This second medication period extended over nine weeks, at which time the drug was again discontinued. Statistical analysis of the material at this time, however, brought to light some new problems, to settle which a third medication period was instituted after a rest period of seven weeks. The dosage this time was at the previous maximum level of forty-five pills daily, and was continued for only five weeks.

In the first medication period detailed studies were made of numerous physiologic processes, including weekly determinations of blood cytology and oxygen consumption rates, and monthly chemical analyses of twenty-four-hour urine samples and of the nitrogenous, sugar, and cholesterol constituents of the blood. Blood pressure readings were taken by a trained nurse on three successive mornings a week at approximately 7:00 A.M.,

*Studies made with the collaboration of the Research Staff of the Worcester State Hospital.

†Read before the Seventeenth Annual Meeting of the Association for the Study of Internal Secretions, Milwaukee, June 12, 1933.

§The extract was generously supplied by Schieffelin & Co. of New York. The method of preparation was previously described (1).

before the patients had arisen, and checked at frequent intervals by a physician. Observations that had been made over a seven months' test period (2) which had ended a few months previously were utilized for initial control material. These studies were continued throughout the succeeding rest and medication periods. During the second interval of non-medication all tests were discontinued. In the final period of medication blood pressure studies alone were made.

The results of the medication on blood pressure are graphically portrayed in Figures 1-4. The means of the three weekly readings on each individual were computed and are indicated on the graphs by the small dots and circles; the mean values for the entire group are represented by large dots. The double line at the beginning (Figs. 1 and 2) signifies that the patients were divided into two groups, one beginning medication a week later than the other. Since one patient dropped out before completion of the study, the data on nine only were utilized. The rise in the systolic pressure was quite marked in each case, although the patients varied somewhat in their response from time to time. A comparison of

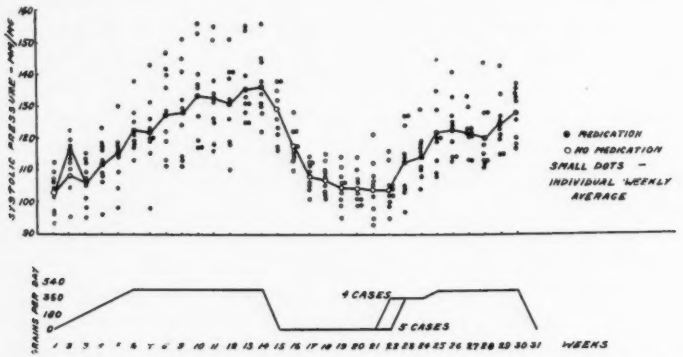


Figure 1. Effect of adrenal cortex medication on systolic blood pressure, first two periods.

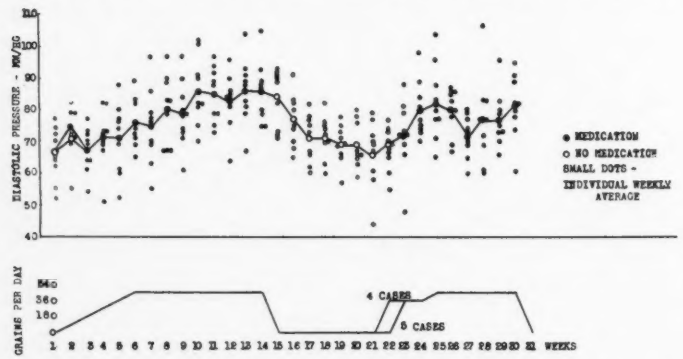


Figure 2. Effect of adrenal cortex medication on diastolic blood pressure, first two periods.

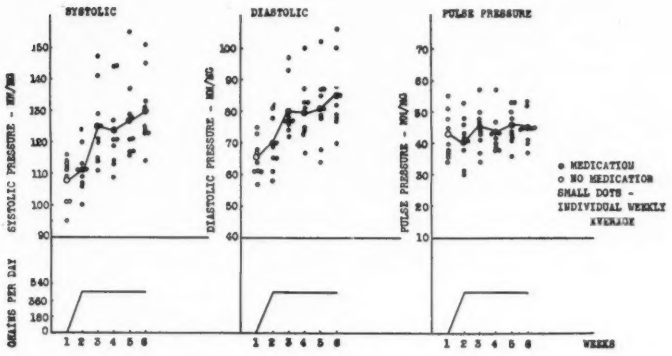
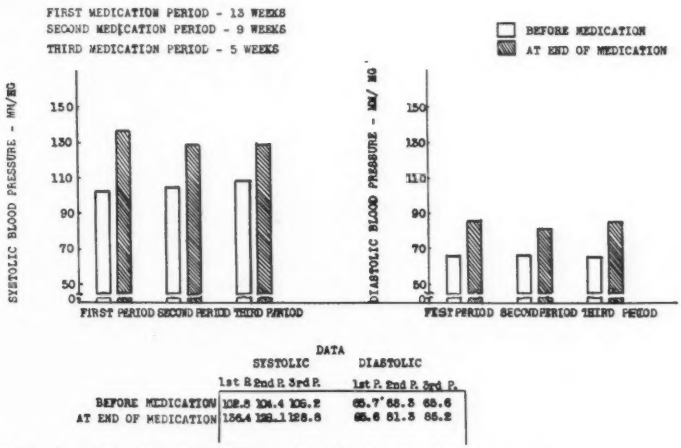


Figure 3. Adrenal cortex—third medication period: Effect of adrenal cortex medication on blood pressure.


FIRST MEDICATION PERIOD - 13 WEEKS
SECOND MEDICATION PERIOD - 9 WEEKS
THIRD MEDICATION PERIOD - 5 WEEKS
BEFORE MEDICATION
AT END OF MEDICATION
SYSTOLIC BLOOD PRESSURE - MM/HG
DIASTOLIC BLOOD PRESSURE - MM/HG
FIRST PERIOD SECOND PERIOD THIRD PERIOD
DATA

	SYSTOLIC			DIASTOLIC		
	1st P.	2nd P.	3rd P.	1st P.	2nd P.	3rd P.
BEFORE MEDICATION	102.8	104.4	105.2	65.7	68.3	68.6
AT END OF MEDICATION	136.4	128.1	128.8	85.6	81.3	85.2

Figure 4. Adrenal cortex—Effect of medication on blood pressure.

the means of the last week of the rest period and of the final week of the medication period shows the mean rise in the systolic pressure to have been 34, 24, and 22 mm., respectively, for the three periods (Fig. 4).

The lesser change in the latter periods may have been due to the shorter duration of medication. On the other hand, it may possibly be ascribed to a change in the physiological status attendant upon the first ingestion of the drug or upon a variation in the potency of the preparation. The rapidity and extent of the elevation of the blood pressure bore a somewhat direct relationship to the dosage, for in the last two periods of medication the slope of the curve was more abrupt than at first when the drug was given in smaller amounts. The material exerted its effect in a very short time for some change was noted within a week after its administration began. Apparently the greater part of the increase in blood pressure under the maximum dosage was attained in approximately three weeks,

although a slight further change was discernible throughout the period of medication. On discontinuing the medication, the fall in blood pressure was rather rapid, the original level being nearly reached in most cases in three weeks.

There was, apparently, a slight residual effect over a longer period of time, for the mean systolic blood pressure at the beginning of the second and third periods of medication was three and five mm., respectively, above the original level. This change is in itself not very significant, but its consistency entitles it to consideration.

The diastolic blood pressure (Fig. 2) exhibited in general a trend parallel to that of the systolic. During medication it underwent an elevation of 20, 11 and 20 mm., respectively, for the three periods. In the second period the diastolic slope exhibited a marked fluctuation. Whether this was connected with the lesser change and was due to anything more than random variation was not determined. In the intervening rest periods, however, the diastolic pressure, unlike the systolic, returned to its original level (Fig. 4).

Similar consistent changes were not found in the pulse pressure. The maximum rises in this case were 14, 10 and 2 mm., respectively, for the three periods. The gradual lessening of the increase in the pulse pressure with each successive period may have been due to the shorter period of medication for, while the systolic pressure continued to exhibit a tendency to rise as the medication continued (although its slope became less after the first three weeks), the diastolic pressure was affected somewhat less rapidly and apparently reached a more stable level in the third week.

Analyses of the material of the first two medication periods disclosed a systematic difference between the readings taken on the ward by the nurse and in the metabolism laboratory by the technician, the values in the latter case being, on the whole, somewhat lower. In these two periods the ward readings and laboratory readings were not taken on the same day, but to make the comparison as valid as possible, the ward reading on the day nearest the basal reading was selected and the two compared. In Figure 5 it is seen that this difference increased with medication and

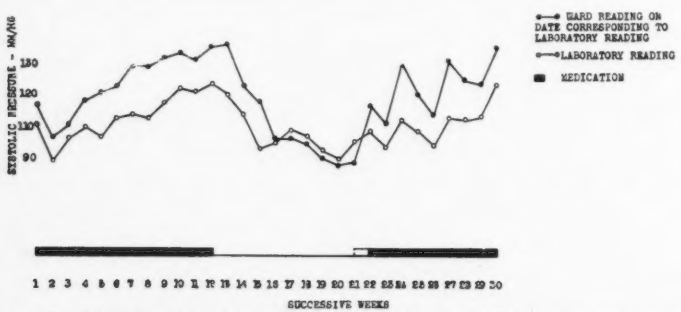

WARD READING ON DATE CORRESPONDING TO LABORATORY READING
LABORATORY READING
MEDICATION
SYSTOLIC PRESSURE - MM/HG
130
120
110
90
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
SUCCESSIVE WEEKS

Figure 5. Adrenal cortex—first and second medication periods: Weekly mean systolic blood pressure of nine patients on the wards and in the laboratory.

diminished as the effect of the drug decreased. To obtain further light on the phenomenon, in the third medication period readings were taken at 7:00 A.M. on the ward, at 8:00 A.M. in the laboratory, and at 9:00 A.M. again on the ward. The results are shown in Figure 6. The 7:00 A.M. and 9:00 A.M. blood pressure readings were practically identical. The laboratory readings, on the other hand, remained consistently below the others, and the difference increased as the medication was maintained. The changes in the difference between the ward systolic blood pressures and the laboratory systolic pressures during medication pursued a curve fitted by the regression equation:

$$y=1.445+1.649x$$

in which x=time and y=difference in pressures. Statistical analysis showed the regression coefficient (1.649) to be significant.

To determine whether the technic or the technician was the decisive factor in causing this difference, various tests were made. The instruments used were mercury sphygmomanometers of a standard make. For

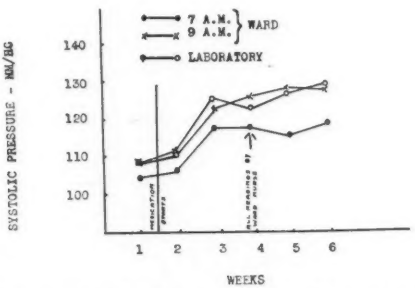


Figure 6. Adrenal cortex—third medication period: Ward and laboratory systolic pessures, weekly mean of nine patients.

purposes of comparison these were connected by a Y tube and various pressures applied. The pressure readings, however, were found to be identical. The observers were then tested by means of a multiple stethoscope. In thirteen patients the differences in the readings of the systolic pressure between the technician and the nurse ranged from +12 to —6, with a mean of +0.62. Thus, while there was some variation between the observers, there was no significant systematic difference. As an additional check, the nurse during one week took the pressures in the laboratory as well as on the ward. The week during which this was done is noted in Figure 6. The readings remained at practically the same level as when the technician had made them.

It would seem, therefore, that whatever factor caused this difference between ward and laboratory readings resided in the environment. It was noted that the wards were noisier than the laboratory, and that, consequently, the opportunity for complete relaxation was less. In addition,

the patients were habituated to the laboratory rooms where they were accustomed to having metabolism determinations and where no painful tests such as venipunctures had ever been performed as on the wards. We were led to the conclusion, therefore, that the lower blood pressures in the metabolism laboratory were due to the relative absence of extraneous stimuli and to the conditioning factors of that environment. The increasing difference between the pressures in the laboratory and on the ward during medication would seem to indicate that the reactivity of the patients was increased by the drug.

In addition to differences between the laboratory and the ward readings it was observed that the readings on the wards changed systematically throughout the day. Those obtained in the evening were higher than the morning readings. These changes are depicted in Figure 7. It will be

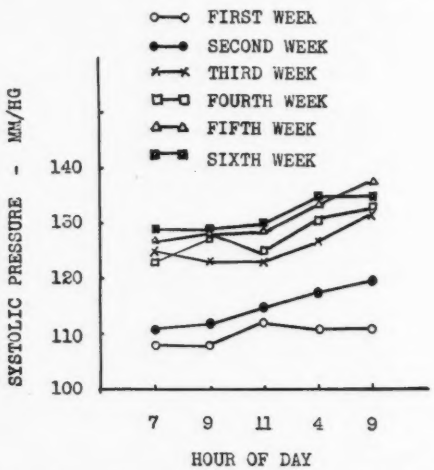


Figure 7. Adrenal cortex—third medication period: Weekly mean systolic pressures of nine patients for different hours of day.

noted that the morning-evening difference became larger as the medication progressed, again indicating increased reactivity of the subjects. The sudden rise in the third week which had been seen in the previous figures (1 and 3) is here again clearly evident.

It was reasoned that if the varying differences between ward and laboratory readings were due to concomitant changes of reactivity of the subjects, other variables than environment should produce comparable effects. This theory was tested by determining blood pressures during various hours of the day in recumbent and standing postures and following a standard exercise. Readings were taken after fifteen minutes' recumbency at 11:00 A.M., 4:00 P.M. and 9:00 P.M. In addition, at 4:00 P.M. on two days each week, following the reading of the blood pressure in the recumbent position, the patient stood up and the pressure was again taken sev-

cral times until a steady level was reached. He then performed a simple exercise which consisted of placing the left foot on a box 18 inches high and bringing the right foot up and down from the floor to the level of the left foot five times in ten seconds, and then withdrawing the left foot. Immediately after the cessation of the exercise the blood pressure level was noted.

In Figure 8 are charted the effects of standard exercise upon the systolic blood pressure, the three graphs illustrating the result of changing from a recumbent ot a standing position (Delta 1); from standing to exercise (D2); and from recumbency to after exercise (D3). The actual differences in the pressures under these conditions are noted on the side of the graph, the numbers from above downwards corresponding to the weeks of medication as indicated in the figures under the graphs. The general tendency was for the difference in the blood pressures in the various posi-

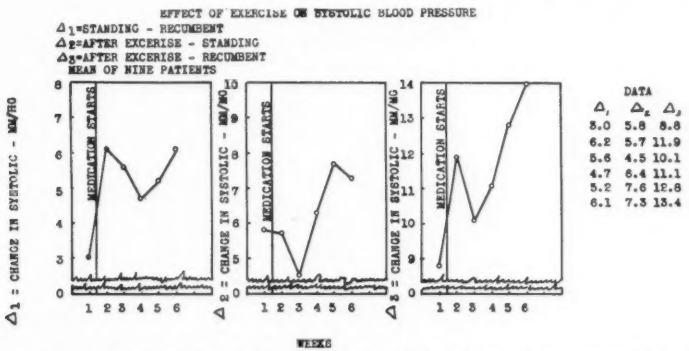


Figure 8. Adrenal cortex—third medication period: Effect of posture and of exercise on systolic blood pressure.

tions to increase, especially after exercise, the aberrations of the third week again being evident. The third graph (D3) illustrating the difference in the systolic pressure in the recumbent position and after exercise is a summation of the other two and exhibits the most marked effect. The change in the diastolic pressure and in the pulse pressure as a result of exercise were also studied. The diastolic level diminished slightly and the pulse pressure ranged higher following exercise as medication progressed. The data elicited served to verify the supposition that the active principle of the suprarenal cortex preparation intensifies the cardiovascular reactivity of the individual.

The effect of the medication upon other physiological processes is summarized in Table I. The data of the whole of the first rest period have been compared with those of the second period of medication. A valid objection may be raised that in the first portion of the rest period, the residual effect of the medication was still present while in the next medication period the influence of the drug was only gradually approaching

TABLE I

ADRENAL CORTEX

Comparison of the Data of Rest Period and Second Medication Period

Variable	Mean Change	Fisher's "t"	Probability	Number of Cases	Significance
1. Weight	+ 0.83	3.670	<0.01	9	X
2. Oxygen consumption	+ 6.56	2.124	0.07	9	
3. Pulse rate	− 4.22	7.226	<0.01	9	X
4. Urine volume	−479.00	1.939	0.09	9	
5. Total solids	− 0.44	0.078	>0.90	9	
6. Total nitrogen	− 1.03	1.378	0.20	9	
7. Urea nitrogen	− 0.98	1.518	0.17	9	
8. Creatinin	− 0.04	1.135	0.29	9	
9. Residual nitrogen	− 0.15	2.290	0.05	9	
10. Urine specific gravity	+ 3.67	3.776	<0.01	9	X
11. Blood velocity	− 2.66	0.112	>0.90	8	
12. Erythrocytes	+26,000.	0.357	0.73	9	
13. Leukocytes	+185.	0.535	0.61	9	
14. Polymorphonuclear leucocytes	+ 0.27	0.214	0.86	9	
15. Sugar	− 3.89	1.805	0.11	9	
16. Cholesterol	− 40.33	10.133	<0.01	9	X
17. Blood non-protein nitrogen	− 0.91	0.081	0.45	9	
18. Urea nitrogen, %	+ 1.56	1.097	0.30	9	
19. Amino acid nitrogen, %	− 0.98	1.306	0.23	9	
20. Uric acid nitrogen, %	− 0.52	2.166	0.07	9	
21. Creatinin nitrogen, %	+ 0.03	0.632	0.56	9	
22. Residual nitrogen, %	− 2.96	1.785	0.12	9	

the maximum obtained. Thus, the contrasts are minimized. The method, though faulty in these respects, gains in the increased frequency of measurements which it utilizes and is probably at least as satisfactory as any technic. The analytical procedure is that of Fisher's "t" (3) in which the conventional assumption is made that in nine cases the value of the criterion "t" must exceed 2.896 to be of significance. In the column marked "Probability" is stated the probability that the change noted was due merely to "random variation." Thus, the increase in weight could be explained as a chance occurrence with a probability of less than one in 100.

The variables showing significant effects by this method are noted in the last column by the letter "x." The body weight and specific gravity

TABLE II

ADRENAL CORTEX

Analysis of Ward Blood Pressures for Three Medication Periods

	Mean Change*	Fisher's "t"	Independent Probability†
Systolic—			
1st period	+33.67	9.174	<0.01
2nd period	+22.22	4.178	<0.01
3rd period	+21.89	6.047	<0.01
Diastolic—			
1st period	+19.89	4.470	<0.01
2nd period	+11.00	2.933	<0.02
3rd period	+19.78	5.835	<0.01
Pulse Pressure—			
1st period	+13.78	4.176	<0.01
2nd period	+10.22	2.740	0.03
3rd period	+ 2.11	1.111	0.30

*The value given is the mean of observations during the last week of medication minus the mean of observation during the week preceding each medication period.

†The total probability increases exponentially with each independent consistent effect.

of the urine were increased significantly, while the pulse rate and blood cholesterol levels were decreased.

Some of the other trends are interesting but in a sample the size of that available are no more than suggestive.

In Table II is presented a summarized statement of the blood pressure data and a study of the "probabilities" of significance by the Fisher method (3).

THE MEANING OF FISHER'S "t"

Let us assume that we have a very large group of numbers from which we can draw samples. We draw a sample of a given size and compute its mean, then we can draw another sample and compute its mean; then we take the difference between these two means. Let us proced drawing pairs of samples like this. Sometimes the first mean of the pairs will be the larger and so the difference will be a positive value, at other times the second mean will be the larger and so the difference will be a negative value. However, if the samples are drawn strictly at random there is no reason why one mean would be consistently larger or smaller than the other, and consequently, in the long run, the average difference would be zero. If we would draw 1,000 such pairs of samples and compute the difference for each pair and then make a frequency diagram of their differences we would obtain a typical "cocked-hat" distribution (Fig. 9).

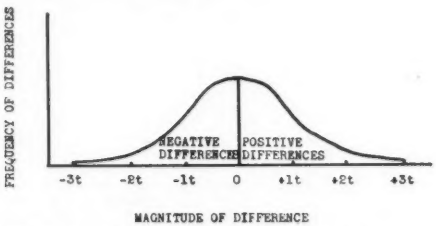


Figure 9. Hypothetical distribution of differences.

The point is that if we know the standard deviation of the original group of numbers then we can compute the standard deviation of the distribution of differences shown above. Not only can we compute the standard deviation but also the limits or extreme values of the above distribution. Now to do this we must have some unit of measurement. Since we wish to apply the method to many different physiological variables the unit must be a general one which will work in all cases. Fisher's "t" is such a unit of measurement and is obtained by dividing the difference in the original units of measurement by a function of the standard deviation in those units. The spread of a distribution of differences depends upon the number of observations in each sample. We wish to know, therefore, the limits of this distribution for the size sample which we have. For the sake of illustration assume that we were using samples of such size that the limits of the distribution of differences was $\pm 3t$. The argument then is formulated thus:

1. If we draw random samples of the specified size, the difference between their means will not be more than $+3t$ nor less than $-3t$.
2. If in any case we get a difference exceeding these limits we conclude that the samples were not random.

Let us apply this general argument to the specific case at hand. The blood pressure readings on nine patients constitute a sample of blood pressure readings drawn from all possible patients. After a period of time we again take readings on these nine patients, and compute the average difference between the readings. Now if nothing of significance has occurred during this interval of time both sets of readings will be random samples of readings and the difference between them will not exceed $\pm 2.896t$ (for a sample of nine subjects $\pm 2.896t$ marks the limits of the distribution of random differences). However, if the obtained difference does exceed $\pm 2.896t$ then we must conclude that the two

samples are not random and this means that something of significance has happened during the interval.

If, during this interval, medication is administered, and the medication has an appreciable effect on the variable under consideration then we expect to obtain a "t" greater than one which would occur by chance.

In reality, of course, the distribution of differences does not have well marked limits. We can only say that certain high values of "t" are very improbable. Statisticians are not agreed upon just what values should be considered "improbable" under random sampling. Consequently for each value of "t" there is given a Probability and this indicates the chances that such a value of "t" would occur under random sampling. If the Probability is 0.02 or less (which means that such a value of "t" would happen no more than 2 per cent of the times by chance) then we say that some factor (the medication in our case) is having an appreciable influence on the variable under consideration.

DISCUSSION

To what extent the glycerin extract we used represents a normal hormone is unknown. We are not aware of its having been used in substitution tests in animals deprived of their adrenals. It has been employed in Addison's disease by Greene (4). His experience was to the effect that the extract significantly improved the subjective condition of the patients but it had no recognizable influence on the objective symptoms. Whether the dosage used was adequate to bring out such influence was not stated. Rogoff (5), on the other hand, has reported favorable results in Addison's disease with his extract, "Interrenalin," which, in its method of preparation, is rather similar to that of the material used by us but with an additional alcoholic extraction. Judgment as to the relative merits of adrenal cortex derivatives is difficult at this juncture because of uncertainty as to the ultimate value of any. Harrop, et al. (6), after considerable experience with cortical extract made by the Swingle and Pfiffner method have expressed doubt of its value except in the treatment of intercurrent shock. In their experience it had no definite effect on blood pressure and only doubtful effect, if any, on weight. The suggestion is obvious that supplementary treatment with glycerin extract in adequate dosage which does influence these functions, might be of signal value.

One of the characteristic features of adrenal deficiency in man is "running down" as the day progresses. It is interesting in this connection to note the gradual rise of blood pressure from morning to evening that was evident in our subjects under treatment with the glycerin extract. Their increased efficiency of cardio-vascular response to change of posture or exercise is also suggestive in this connection.

One of our purposes in the continuation of the study was to obtain further evidence regarding optimal dosage. There was a suggestion at the end of the third week of the second medication period (Fig. 1) that the pressure curves were flattening off on 360 grains a day but an even more pronounced flattening occurred during the sixth and seventh weeks on 450 grains, whereas the ascent was re-established with continuation of the same dosage. The evidence as a whole indicates that we had not reached the upper effective limit of dosage even at 450 grains. Then, too, the curves—

at least of systolic pressure (Figs. 1 and 5) and of reactivity (Fig. 8)—were still ascending on a fixed dosage when the medication was discontinued. It would seem, therefore, that the treatment could have been profitably continued both for longer intervals and at higher dosages.

These results, however, are not necessarily directly transferable either to non-psychotic subjects or to those suffering from Addison's disease. We have frequently had occasion to note high thresholds to gland medication in schizophrenics. For example, we have given desiccated thyroid in dosage up to 60 grains a day and obtained only moderate effects (7). Likewise account must be taken of the fact that subjects of a given glandular deficiency are more reactive to corresponding medication than are normal subjects. While the schizophrenic patient characteristically presents a picture of generalized hypo-metabolism suggestive of a condition of mild adrenal deficiency (8) we have no satisfactory evidence of the actual participation of the adrenals in the genesis of the psychosis. Of negative tenor is the fact noted in these studies that the psychosis was not significantly ameliorated during the progress of the treatment.

A final point worthy of comment is that the glycerin extract used was notably stable. The first lot employed had been in our possession several months before it was used but proved to have been quite as potent as other freshly prepared lots that were used subsequently.

The adrenal cortex plays an important rôle in the bodily economy. The fact that glycerin extract is easily prepared and is of proved and relatively high potency would seem, therefore, to render desirable further extensive investigations of its properties. The problem is commended to others who have facilities for such studies.

SUMMARY

Nine schizophrenic patients have been treated during three periods, each with glycerin extract of adrenal cortex. Conclusive evidence of the potency of such extract was secured.

The dosage varied at different times from a fresh-gland equivalent of 30 grains (2 gm.) to 450 grains (30 gm.) daily. The medication periods were 13, 9, and 5 weeks, respectively.

The systolic blood pressure was increased on an average, 34, 24, and 22 mm. Hg., respectively, during the three medication periods. There was a slight residual pressor effect maintained during the intervals between medication periods.

The diastolic pressure was increased 20, 11, and 20 mm. Hg., respectively, in each period.

The cardio-vascular reactivity of the patients to environmental excitement, to change of posture and to exercise was increased during the medication period. The effect became progressively greater from 7 A.M. to 9 P.M.

The body weight was slightly though significantly increased as was the specific gravity of the urine. The pulse rate and the blood cholesterol level seemed to have been significantly lowered.

Changes in several other functions were suggestive but the data were not sufficiently numerous to permit accurate judgment.

The evidence secured is to the effect that neither maximum effective dosage nor duration was employed.

It is concluded that glycerin extract of adrenal cortex is a potent medicament for the elevation of blood pressure and for increasing cardiovascular reactivity. Its other properties demand further investigation.

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CONCERNING ANTERIOR PITUITARY HORMONES*

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The data presented here supplement a preliminary statement (1, 2) and a fuller account soon to be published (3) concerning the isolation and physiological actions of an anterior pituitary hormone which is now known as "prolactin."

Competent investigators of the anterior pituitary rightly require very exacting proofs that hormones other than those first identified with "growth" and "sex-maturity" responses are formed in the anterior pituitary; and this insistence is concurrent with their ready recognition of some twenty physiological effects—primary, secondary or otherwise—already known to be provokable with anterior pituitary substances; but they realize that even a single (e.g., sex-maturity) hormone—with the inclusion of differences incident to stage of life cycle and to amounts administered—may conceivably evoke twenty responses of primary, secondary or other nature. Before any reaction or response to an "extract" can be considered to indicate a hitherto unknown pituitary principle it is necessary to supply evidence that neither the growth nor sex-maturity principle, nor various combinations of these two hormones, will elicit that response. This is essential. Before any active substance extracted from the anterior pituitary can be said to be different from growth and maturity principles, and entitled to a new name, that substance must have been tested in suitable amounts on *adequate test-objects* for the responses characteristic of the growth and maturity principles. All this is essential.

At present it appears that only our laboratory claims to have fulfilled, or to have attempted to fulfill, these requirements as they relate to the separateness and isolation of the principle which evokes the now long known lactation and crop-gland responses. During most of the past two years we therefore have been continuously confronted with whatever difficulties are associated with the testing of a pituitary constituent for possible contamination with growth hormone and with sex-maturity hormone. We have reserved a discussion of "growth hormone tests" for first place in this paper.

THE DIFFICULTIES AND UNSATISFACTORY NATURE OF TESTS FOR GROWTH HORMONE

Omitting all except this passing reference to the complexity of the impulses to, and limiting factors of, normal growth processes, we at once

*Read before the Seventeenth Annual Meeting of the Association for the Study of Internal Secretions, Milwaukee, June 13, 1933.

encounter objections to the use of a normal intact animal of any age or sex for growth hormone tests; we ourselves have used intact doves and pigeons almost exclusively, but we have not trusted—nor do we ask others to trust—gains or losses of weight in these animals as indicating the presence or absence of growth hormone. A prime difficulty rests on the probability that though a quantity *n* of pure growth hormone would give a maximum growth effect, this same quantity when mixed with large amounts of the gonad-stimulating and thyroid-stimulating principle or principles may exhibit—at least as an early response—(a) little growth, (b) no growth, (c) actual loss of weight. Growth hormone thus admixed may be introduced into doves and pigeons without a weight increase response. Short term (up to two weeks) injections of gonad-stimulating fractions which, because of the method of preparation, should contain some growth hormone, and proved by our assays to have resulted in marked thyroid enlargement, have usually and repeatedly led to loss of weight in these animals; we have observed similar results in guinea pigs.

It should be noted that many of the birds used by us belong to "thyroid races" selectively bred and established on the basis of thyroid size (4), and that current studies are showing that the basal metabolism varies among these races; it is therefore entirely probable that one and the same mixed extract (growth plus thyroid-stimulating) would have very unequal and probably unlike effects depending upon whether a bird of hypothyroid or hyperthyroid race is used in the test. Further, it can scarcely be doubted that unrecognized differences of thyroid activity exist among the animals used by other investigators. The action of relatively pure growth hormone on thyroidectomized animals is still unexplored. Finally, it is also conceivable that the injection in quantity of another anterior lobe hormone than the growth hormone might result in an increased output of growth hormone from an intact animal's own pituitary.

Hypophysectomized animals (rats) have been used in growth hormone tests by several workers (Smith, Evans, Van Dyke and Wallen-Lawrence, Lee and Schaffer, Collip), and since we have not attempted to prepare or study directly the growth hormone we must accept the merits of the hypophysectomized animals as stated by these investigators. We are, however, fully aware of a real objection to accepting the whole, or any specified part, of the body growth that here follows the injection of a pituitary extract as a response to the growth hormone. In such an hypophysectomized test animal the thyroids, gonads and adrenals become definitely subnormal, and a contaminating substance (not growth hormone) which would raise the thyroids to their normal functional level would almost certainly (except in senile animals) yield also some increase in body weight. Among the preparations of growth hormone now available—and tested for other pituitary contaminations by us (3)—our data show that they all, with the probable exception of that of Collip, Selye and Thomson (5), enlarge the thyroids of doves and pigeons; and we now believe this enlargement is a

specific thyreotropic effect. The positive thyreotropic response (thyroid enlargement) to these "growth" preparations was also usually, but not quite always, accompanied by an unquestionable gonadotropic response (6). It is probably true that the whole of the body growth which would follow the administration of pure growth hormone, or of that hormone free of thyreotropic action, can be attributed to the growth hormone; but, even when hypophysectomized animals are used, this scarcely affects present difficulties of testing other pituitary preparations for contamination with growth hormone. Perhaps animals deprived of both pituitary and thyroid are required for these tests.

It nevertheless appears that the use of the body growth test, on certain suitable animals, has enabled a few investigators to effect a high concentration of the growth-promoting principle along with quite low concentrations of principles giving other specific responses. If this is appearance merely, not reality—if a very high concentration of the growth principle really antagonizes some other pituitary principle in low concentration in a mixture—the consequences are fairly devastating. In our own differentiation of the effects of prolactin from those of the growth hormone, in addition to things elsewhere adequately stated (3), we have utilized preparations shown by others to have high concentrations of the growth-promoting principle, and proved by us to have little or no power to give the crop-gland and lactation responses; the high content of growth principle was attested by others who utilized the currently accepted growth-promoting effect on (chiefly) hypophysectomized rats. The responses to prolactin—particularly that of the crop-gland—accurately, quantitatively and unfailingly measure and identify this hormone over a very wide range of dosage. The test for prolactin is highly satisfactory. We believe that present uncertainties and difficulties with the growth hormone test—particularly in mixed pituitary preparations—is now the greatest single obstacle to further successful research on the functions and chemistry of the anterior pituitary gland.

DIFFERENCES IN HORMONAL CONTENT AMONG VARIOUS PREPARATIONS OF GROWTH HORMONE

The full value of the data of Table 1 will be obtained only when examined in connection with Table 1 of another publication (3). The present data materially supplement the factual basis of the conclusions drawn in the earlier publication, they provide for the first time some values obtained on common pigeons, and for the special purposes of this paper they permit several comparisons of five important types of preparation of the growth hormone.

Though the animals on which these bio-assays were made may not reliably indicate the relative amount of growth hormone in the different preparations it is to be remembered that these preparations have all been shown by current tests on other animals to have a high content of growth hor-

TABLE 1

SHOWING THE ANTERIOR PITUITARY HORMONES ADMIXED WITH THE HORMONE PREPARATIONS OF VARIOUS INVESTIGATORS—TOGETHER WITH RESPONSES IN BODY WEIGHT AND IN CERTAIN ORGANS

Dosage				Age of Bird	Change in Body Weight	Testes*		Thyroid		Liver		Crop Glands	
Preparation		Cc. per Day	Duration			Test	Control	Test	Control	Test	Control	Test	Control
Kind	Number												
			Days	Months	Grams	Mgms.	Mgms.	Mgms.	Mgms.	Grams	Grams	Mgms.	Mgms.
Antuitrin G..... (Growth hormone) (Parke, Davis Co.)	5052A	0.75	5	2.9	294+56	125.7	40	52.3	39.2	10.66	4–7	2.785	700[1]
		0.75	5	2.4	279+35	56.8	27	40.1	39.2	11.34		2.580	
		0.75	5	2.3	273+33	60.0	25	38.6	39.2	10.45		1.910	
		0.75	5	2.8	238+33	(25.1)	(35)	35.7	39.2	10.20		1.600	
		0.25	4	3.2	151+ 4	(19.7)	(26)	51.6	42.0	6.43	2–4	0.820	400[1]
		0.5	4	3.1	151+11	(17.5)	(34)	24.4	42.0	4.36		1.040	
Growth hormone..... (Lee and Schaffer)	31	0.6	5	2.5	245+52	45.2	29	49.1	39.2	19.62	4–7	0.800	700
		0.6	5	2.4	233+40	64.0	27	48.7	39.2	9.27		0.565	
		0.6	5	2.3	245+45	37.8	25	57.9	39.2	13.75		0.650	
		0.6	5	2.3	260+34	38.0	25	86.9	39.2	15.17		0.640	
	00	0.5	4	2.6	155+13	(16.3)	(17)	30.9	19.4	5.32	2–4	0.523	400
		0.5	4	13.4	174+ 2	1595.0	Ad.	42.0	22.0	5.17		0.980	500
		0.5	4	14.2	138+12	930.0	Ad.	28.7	18.0	3.75		0.860	
Phyone..... (Van Dyke and Wallen-Lawrence)	..	0.8	5	2.8	137+ 1	(18.9)	(19)	29.3	12.5	4.42	2–4	0.430	400
		0.4	7	14.0	160+14	(490.0)	Ad.	41.7	15.0	12.05		0.360	500
Growth hormone..... (Evans, 1931 method)	Own	0.5	6	2.9	136+ 4	(23.4)	(20)	24.5	18.8	4.19	2–4	1.790	400
		0.5	6	2.5	144+ 4	(10.5)	(16)	26.4	15.9	4.38		1.430	
Growth hormone..... (Collip, et al.)	Q16	0.5	8	18.4	148+ 7	1850.0	Ad.	32.5	18.0	2.48	2–4	0.640	500
		0.5	8	15.3	160+ 9	1225.0	Ad.	28.0	21.5	3.37		0.460	

*Weights of ovaries are in parentheses.

[1]These are considered maximum control values for the two glands. The common pigeons used (tipplers) are of the smallest race available to us.

mone. All of the 19 tests tabulated here, though not quite all tests made with these preparations, also show some increase in body weight. We may first compare the effects of two preparations which were tested on the same race (tipplers) of common pigeons (birds weighing 230-300 grams). With nearly comparable dosage antuitrin G gave a somewhat smaller growth increment (14.5 per cent) than did the preparation of Lee and Schaffer (17.4 per cent). In this latter and better growth preparation *prolactin* is scarcely detectable; but it is present in large quantities in Antuitrin G. That the gonad-stimulating hormone is present in both of these preparations is clearly shown by the seven tests made on immature males. These results further indicate that the antuitrin G contained as much or slightly more of the gonad-stimulating (sex-maturity) hormone than did preparation No. 31. Lee and Schaffer's preparation No. 00 was made by a variation in procedure (personal communication) and contained notably more gonad-stimulating hormone and more prolactin than their other preparations (three tested by us).

Among the other three types of preparation we find similar differences. Phyone appears in these and other tests (3) to yield a greater increase of weight in our animals than does the Evans hormone, but it has only traces of *prolactin* while the Evans type of hormone (prepared by us) contains very large quantities of prolactin. Other data (3) have shown that though both of these preparations also contain gonad-stimulating hormone the larger amount was found in phyone; also, that the Collip preparation is free of detectable amounts of gonad-stimulating hormone and contains only small amounts of prolactin.

Though Table 1 supplies only a few weights of thyroids of treated animals, and though the control weights are quite variable, it can be concluded on the basis of these and additional cases published elsewhere (7) that phyone, the Lee and Schaffer, and the Evans hormones all contain a principle which causes enlargement of the thyroids of doves and pigeons. Other tests with Collip's preparations have indicated no thyroid enlargement. Much experience with prolactin has indicated that it, too, does not enlarge the thyroids of our animals. In a great predominance of nearly 700 tests made by us thyroid enlargement has been found associated with the gonad-stimulating hormone. We are much impressed by this association but admit that it has not been proved that gonad and thyroid stimulation are responses to the same pituitary principle.

The effect of most of these preparations on the liver is very marked. Only the preparation of Collip, Selye and Thomson fails here (as in still other tests) to cause a rapid and pronounced increase in liver size: and, all in all, this preparation is least contaminated with hormones other than growth hormone. This and a fuller survey of our data, have led to the view (7) that, though enlarged livers result from abundant or excess dosage with most of the pituitary preparations hitherto used, this is a specific response to no pituitary hormone but is a non-physiological (patho-

logical) response to unusual quantities of two or more potent hormones which never normally thus coexist in the blood. The present data afford some further evidence for that view, and a mixture of the growth and gonad (thyroid)-stimulating hormones seems to be an effective agent. For clinical use perhaps these data suggest the desirability of purification and separate administration of these two hormones. Probably, however, few human subjects are likely to receive the high and continuous dosage (of mixed extracts) which we consider the basis of this unfavorable response of the liver in our tests.

SPECIFIC ADVERSE EFFECT OF PROLACTIN ON THE MATURE TESTIS

Hitherto only two specific responses to prolactin were known—the lactation and crop-gland responses. In Table 2 we give results of tests of the action of prolactin on the testes of mature ring doves. The very few

TABLE 2

EFFECT OF PROLACTIN ON TESTIS SIZE IN ADULT RING DOVES

Preparation	Dosage		Number of Tests	Body Weight Change	Weight of	
	Mgm. Daily	Duration			Crop Glands	Testes
		Days		Grams	Mgm.	Grams
			Control Series			
Control*	5*	7	10	162 − 5	425	1.31
			First Series (less potent prolactin)			
34	0.25	6	5	153 − 1	377	1.24
34	1.	5	5	156 − 0	648	0.93
34	2.5	5	7	159 + 5	1485	0.79
34	3.5	4	5	159 + 5	986	0.74
34	10.	4	4	146 +14	1198	0.60
34	10.	7	3	146 +16	2575	0.20
			Second Series (more potent prolactin)[1]			
119	0.014	7	3	151 − 3	440	1.14
119	0.025	4	1	138 − 9	600	1.12
119	0.043	8	2	152 + 1	3100	0.77
165	1.	11	2	150 +11	2890	0.74
74	2.5	11	1	154 + 3	1160	0.17
74	4.	10	1	147 +10	2550	0.19
58	5.	13	2	142 +25	2485	0.09

*Injected with an acid-soluble iso-insoluble extract of muscle.
[1]Daily dosage given in 2 or 3 injections.

tests we have made with mammalian testes (guinea pigs) gave indefinite results. We believe that our tests on doves prove that prolactin has specific power to induce involution of the mature testis. The more conclusive evidence that neither the growth-stimulating nor gonad-stimulating hormone is responsible for this strikingly adverse effect is given in Table 3. Since, however, in the preparation of most of the prolactin samples used in these tests we did not employ all recognized means of separating or destroying the growth hormone we are unable to state positively that this response (like that of the liver noted above) is not an effect ascribable to simultaneous administration of growth and prolactin hormones.

The evidence that prolactin can specifically tear down that part of testis development which the gonad-stimulating hormone specifically aids in building up (gonads develop to a certain stage before any sex-maturity hormone is secreted) is a point with very interesting associations. First, the pioneer investigations with quite impure anterior pituitary extracts showed that their use leads to the luteinization of ovaries, but it has not been possible to identify the specific pituitary principle which evokes this response. Luteinization may turn out to be essentially gonadic (ovarian) regression as opposed to growth (8), and prolactin a specific cause of this regression. But this regression—a response to adverse influence—may also result from other non-specific adverse agencies (e.g., prolan or "luteinizing" substance from urine, etc.). It may be found also that the production or release of gonad-stimulating hormone by the pituitary is completely stopped by the presence of prolactin in the blood. Second, something adverse to continued full gonadic activity certainly accompanies the incubation period and persists for a shorter or longer period thereafter in all birds which nest their eggs; otherwise egg-laying should continue. We now have some evidence that prolactin begins to enter the blood stream of pigeons as soon as they begin to incubate eggs, and Champy and Colle (9) have stated that both the testes and ovaries of these birds suffer marked rhythmic diminution of size during the course of the incubation cycle. Again, in mammals, certainly that truly progressive phase of ovarian activity which is promoted by the gonad-stimulating (sex-maturity) hormone is usually in abeyance during both pregnancy and lactation. We now know that the lactation phase is initiated and may be sustained by prolactin. Whether during pregnancy also the ovary is or is not repressed by prolactin is now pure conjecture. Previously it has been supposed that the above noted phenomena in both birds and mammals could be accounted for, at least in part, by a mere cessation or reduction in the output of gonad-stimulating hormone. This newly found capacity of prolactin to depress the mature testis demonstrates that this hormone enters as a positive factor into certain phases of this broad question.

Data dealing with the effect of prolan on the mature testis (Table 3) have some bearing on the subjects just discussed. These data indicate that the action of prolan is distinct from that of growth, gonad-stimulating and prolactin hormones. Its action on these mature testes is one of repression, not of growth acceleration; but in the samples and dosages used by us this repression is much less intense than that following high dosage with prolactin. That prolan (antuitrin-S) is wholly distinct from prolactin is proved by the complete incapacity of prolan to induce the crop-gland and lactation (3) responses. Weights of crop-glands of adult ring doves in excess of 500 or 550 mgm. declare the presence and action of prolactin; lesser weights show the absence of quantities of prolactin detectable by this highly sensitive test. Other unpublished data, obtained in association with Mr. E. L. Lahr, show that though earlier samples of Antuitrin-S (Parke,

Davis Co.) were without true gonad-stimulating effect on the immature bird testis the more recent preparations do give this effect; also that prolan obtained through the courtesy of the I. G. Farbenindustrie Aktiengesellschaft (Elberfeld) does not show this effect.

TABLE 3

EFFECT OF GONAD-STIMULATING AND GROWTH HORMONES, AND OF PROLAN, ON TESTIS SIZE IN ADULT RING DOVES

Preparation	Dosage		Number of Tests	Body Weight Change	Weight of	
	Mgm. Daily	Duration			Crop Glands	Testes
		Days		Grams	Mgms.	Grams
Control*	5*	7	10	162 – 5	425	1.31
			Gonad-stimulating (Maturity) Hormone			
82	1	8	2	166 – 6	542	1.39
82	2	7	2	161 – 8	470	1.43
126	2	11	5	147 – 6	466	1.58
139	5	9	1	174 – 17	580	2.28
139	10	7	3	155 – 11	561	1.94
			Growth Hormone (Collip)			
Q16	1	8	2	154 + 8	550	1.54
Q40	2	10	2	150 + 12	600	1.40
			Prolan and Antuitrin S			
5273-B	5[1]	6	2	1 – 5	378	1.35
5286-B	5[1]	6	3	151	382	1.37
5170-A	20[1]	7	2	155 – 7	395	0.97[2]
5286-B	30[1]	6	4	163	448	1.51
5273-B	40[1]	9	4	152 – 5	420	1.08
Prolan	20	11	5	159 – 2	466	0.91[2]

*Injected with an acid-soluble iso-insoluble extract of muscle.

[1]Rat units; because of progressive deterioration in samples it is not certain that the amount of order or dosage is correctly stated here. Numbers are Parke, Davis designations.

[2]Test made during the autumn when the untreated testis is probable .2-.3 gr. less than usual weight.

GOOD GONAD-STIMULATION IN THE ADULT TESTIS AND OVARY

We have noted elsewhere (3) that the gonad-stimulating hormone is simultaneously recovered incidental to certain methods used in the preparation of prolactin and that the sex-maturity hormone thus recovered greatly accelerates testis growth in immature doves and pigeons. We can now show (Table 3) that such preparations (No. 82), and other similar ones (Nos. 126 and 139), which have been further subjected to Collip's method of calcium phosphate precipitation of the growth hormone, are highly active also on the *mature* testes (Table 3) and ovaries (Fig. 1) of adult ring doves.

Concerning the capacity of these preparations (which usually exhibit only traces of prolactin even in very high dosage) to carry the testis *beyond its normal size* we would note that there is apparently a limit beyond which an increase of daily dosage brings no increased response; and that still greater size increase in the testis is probably to be sought in moderate daily dosage continued over a longer lapse of time. It seems to us that preparations such as these—not prolan—should now be given their prelim-

inary clinical tests in cases in which an acceleration of the progressive activity (not luteinization) of the gonad is desired in either the male or female.

The effects upon the ovary recorded in *A* of Figure 1 were obtained by 14 daily injections (3 mgm. each; No. 139) administered while this female was completing her term of incubating eggs. During this period the ovary should remain quiescent—as was found and here shown (Figure 1, *B*) in an uninjected control. Normally only one, two, or at most three ova will enter the short final growth period which precedes ovulation; actually, however, 26 such ova were thus developed even during incubation (a period of prolactin release) by the injection of a good preparation of the gonad-stimulating hormone.

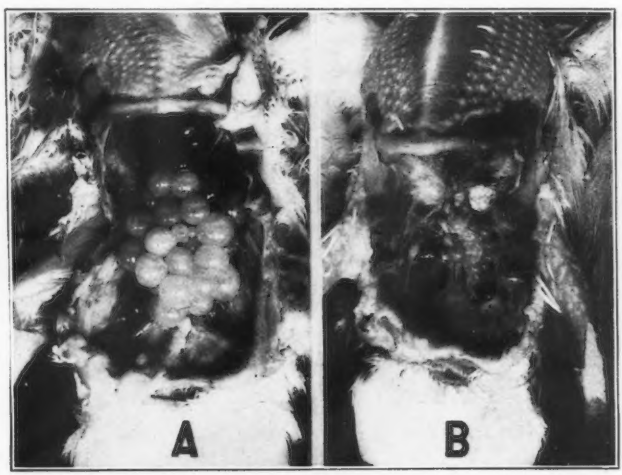

Figure 1. Effect of gonad-stimulating hormone on adult ring dove ovary (see text). *A* injected; *B* control. Both killed at end of incubation cycle and crop-glands of *both* doves fully activated.

SUMMARY

In a summarizing article an attempt is made to state the requirements now indispensable to a demonstration of the existence of an anterior pituitary hormone other than the growth and sex-maturity principles.

The present unsatisfactory nature of tests for the growth hormone is discussed, and the conclusion is drawn that difficulties and uncertainties of this test—particularly in the all-important mixed pituitary preparations—is now the greatest single obstacle to further successful research on the functions and chemistry of the anterior pituitary gland.

Data are given which supplement other publications dealing with bioassays of currently used preparations of the growth hormone. These bioassays provide independent evidence of the individuality and discreteness

of growth, gonad-stimulating, and prolactin hormones in the anterior pituitary.

An additional specific response to prolactin, or possibly to this hormone plus growth hormone, has been found. This hormone induced rapid involution in the mature testes of ring doves. Periodically diminished gonadic activity—during incubation in birds, during pregnancy and lactation in mammals, and the phenomena of luteinization of ovaries—all require reconsideration in the light of this positive action of a pituitary hormone in causing regressive phenomena in the mature gonad. It does not necessarily follow that the minute testis of the immature bird is similarly affected by prolactin.

Preparations of the gonad-stimulating hormone have been shown to induce growth in mature testes and ovaries to far beyond their normal size limits. Such preparations, rather than prolan, should now be given careful clinical tests in cases where increased growth and formation of reproductive elements are desired in either male or female gonads.

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INVERTED SUGAR TOLERANCE CURVES IN A CASE OF ADDISON'S DISEASE

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During the past several years many investigators have called attention to the increased tolerance for carbohydrate seen in Addison's disease. The fasting blood sugar in this condition was noted to be low by Janny and Isaacson (1), Porges (2), Rowntree (3), and others, while other investigators have noted essentially normal fasting levels (Longcope, 4). Rowntree (3) and Chapman (5) have remarked on the diminished hyperglycemia following administration of glucose in patients suffering from this disease. Wauchope (6) has recently summarized the problem of hypoglycemia, and has noted the occurrence of high tolerance in diseases of the suprarenal glands. This latter author has pointed out the bizarre symptoms that may accompany low blood sugars and increased tolerance to carbohydrate. Ramsbottom and Eastwood (7) have also pointed out the peculiar mental symptoms that sometimes accompany low blood sugars.

Although reports of blood sugar studies in Addison's disease are numerous, the author has been unable to find any instances in which there has been an actual inversion of the sugar tolerance curve. The following case is presented because of the unusual blood sugar reactions obtained, in which there apparently was a sufficient preponderance of insulin activity actually to invert the sugar tolerance curves.

Case Report. Patient A. N. Female, 47 years of age; admitted first on November 20, 1932.

The patient was referred to my service by a psychiatrist to whom she had been taken by her son. She had no complaints except a tendency to fatigue readily, some general malaise and insomnia. Members of her family stated that she had been acting queerly for several months. She frequently said things which had no meaning to them and at times would move around restlessly. Recently she had been getting up at night and walking around in the village streets because she could not sleep. Her appetite had been poor for about three months. The patient was a housewife and had no unusual habits. She has five living children and had one abortion at three months during the course of a fever. Her past medical history included typhoid fever three years ago, and malaria two years ago. According to her present medical history she stated that about two years ago she began having some mild headaches, insomnia and general weakness. Several physicians were seen, various medications were prescribed, but no relief was obtained. She was also seen by a psychiatrist, who, on careful examination, decided that she was not in need of sanatorium treatment. Except for the headaches there had been no pain. There was no history of cough, gastrointestinal disturbances, worm infestation, or urinary disturbances. Weight had decreased. The menopause had occurred two years previously at about the time of the onset of her present symptoms.

Physical examination revealed a moderately well-nourished female, approximately 45 years of age. She was quiet, disinterested in her surroundings and conversed rather unwillingly. Her face and hands were definitely pigmented, the color simulating a dirty bronze. The temperature was 37° C.; pulse, 80; blood pressure, 85/45. The eyes were normal in all respects as were the ears,

nose and tongue. There were a few carious teeth with a moderate degree of pyorrhea. There was no hyperemia of the pharynx and no pigmentation of the buccal mucosa. No cervical glands were palpable and the thyroid gland was not enlarged. The chest was normal in appearance. The lungs were normal. The heart was of normal size with regular rhythm, sounds of moderately good quality, and no murmurs. The abdomen was normal in appearance, the spleen was "one finger palpable," the liver and kidneys not palpable. The extremities all showed pigmentation similar to that on the face. At first it looked as if the skin were simply dirty, but closer examination revealed a definite dirty bronze pigmentation. It was distributed over the dorsum of both forearms and hands and was not so marked on the volar aspects. There were three round areas on the forearms where there was no pigmentation. The legs were similarly pigmented below the knees. Slight pigmentation was seen on the trunk. The deep reflexes were all present. Muscular power was poor. There were varicosities on the right thigh and leg.

Examination of the blood revealed 4,260,000 erythrocytes, 8,000 leucocytes, 80 per cent hemoglobin, 73 per cent polymorphonuclears, 19 per cent lymphocytes, 5 per cent large mononuclears, 3 per cent eosinophiles. The urine was acid in reaction, the specific gravity, 1.030; it showed a faint trace of albumen but no sugar or acetone; microscopic findings were normal except for epithelial cells. Blood Wassermann and Kahn tests were negative. The blood cholesterol was 200 mgm./100 cc.; blood urea nitrogen, 15.2 mgm.; blood sugar (fasting), 74 mgm. Lumbar puncture revealed an essentially normal spinal fluid with negative Wassermann and Kahn reactions and a normal colloidal-gold curve.

In view of the low blood pressure, pigmentation, general weakness and history of the patient, it was decided to make a sugar tolerance test. On December 1 she was given 1.75 grams of glucose per kilo of body weight, after a fasting specimen was taken. The curve obtained was completely inverted as is seen in the accompanying table (Table 1). The fasting level was 73 mgm./100 cc.; the 30-minute level, 57 mgm.; the one-hour level, 28 mgm.; and the two-hour level, 73 mgm. During the test there were no untoward symptoms. The patient felt quite as usual during the entire procedure. It was felt that something might possibly have gone wrong with the sugar determinations and the tolerance test was repeated the next day. The procedure throughout the second test was exactly the same and the results were essentially similar to those obtained on the first occasion. The only difference of note in the second curve was a delay in the fall of the curve (see Table 1).

TABLE 1

SUGAR TOLERANCE TESTS ON PATIENT A. N., SHOWING MARKED INCREASE IN SUGAR TOLERANCE AND ACTUAL INVERSION OF CURVES IN FIRST THREE TESTS

Date	Fasting Spec. Mgm. Glucose Per 100 cc.	½ Hour Spec. Mgm. Glucose Per 100 cc.	1 Hour Spec. Mgm. Glucose Per 100 cc.	2 Hour Spec. Mgm. Glucose Per 100 cc.
Dec. 1, 1932.....	73	57	28	73
Dec. 2, 1932.....	78	80	46	63
Dec. 6, 1932.....	74	62	90	49
Feb. 14, 1933.....	75	105	72	80
Feb. 23, 1933.....	75	75	79	79

A basal metabolism test on December 4 gave a value of minus 19 per cent. In view of the fact that basal metabolism is normally somewhat low in this region (Turner, 8), the value obtained represents about minus 29 per cent when corrected to our ordinary American standards.

A third check sugar tolerance test was made on December 6, with a curve as noted in Table 1. All blood sugar determinations were made by the Benedict method (Benedict, 9).

The patient was diagnosed as having adrenal insufficiency (Addison's disease) with associated relative hyperinsulinism. She was discharged from the hospital on December 6, after having been placed on a regime in which she received six tablets of Parke, Davis Suprarenal extract daily, plus the adrenal tissue from two sheep freshly killed daily. (This latter was easy to obtain as mutton is the most common meat utilized in this region.)

Throughout her stay in the hospital her blood pressure had been continuously low, the systolic pressure ranging from 80 to 85, and the diastolic pres-

sure from 40 to 55 millimeters mercury. She was seen again at the end of two weeks and reported some slight improvement. She was sleeping better than formerly but the weakness and general lack of interest in life remained about the same. She was advised to continue the same regime together with small doses of strychnine (2 mgm. daily).

On February 13, 1933, she was readmitted to the hospital for further study. There was no marked change in her condition except that the blood pressure on this occasion was about 95/60. The differential blood count at the time of this admission showed 37 per cent polymorphonuclears, 54 per cent lymphocytes, 5 per cent large mononuclears, 3 per cent eosinophiles, and 1 per cent basophiles. A twenty-four-hour urine specimen examined chemically showed no creatine, 0.481 gram of creatinine, 0.28 gram of phosphates. A subsequent urine examination revealed 0.767 gram of creatinine, 0.368 gram of phosphates and no creatine in the twenty-four-hour specimen. Basal metabolism on this occasion was minus 6 per cent (corrected to minus 16 per cent). A tuberculin test was made which gave a strongly positive reaction after six hours. A recheck of the differential blood count on February 15 showed the same findings as on admission two days earlier. A glucose tolerance test on February 15 gave a curve in which the fasting level was 75 mgm./100 cc., with the maximum rise 105 mgm. at the end of the first half hour. A blood phosphorus curve taken at the same time gave the following values: fasting level, 2.88 mgm./100 cc.; thirty-minute level, 2.88 mgm.; one-hour level, 2.78 mgm.; two-hour level, 2.64 mgm.

All medication was discontinued after her admission on February 13 and a glucose tolerance test repeated on February 23. This revealed 75 mgm/100 cc. in the fasting and the half-hour specimen, 79 mgm. in both the one-hour and two-hour specimens. (Table 1.)

In order to determine whether rate of absorption from the gastrointestinal tract might be a factor in the problem, it was decided to make an intravenous glucose tolerance test on February 17. One gram of glucose per kilo of body weight was given intravenously (25 per cent solution) after the fasting specimen was taken. The resulting curve showed a blood sugar level of 71 mgm./100 cc. in the fasting specimen with a rise to 408 mgm. at the end of 15 minues, 376 mgm. in thirty minutes, 65 mgm. at the end of the first hour, 47 mgm. at the end of ninety minutes, and 59 mgm. at the end of two hours. Control intravenous glucose tolerance tests were run on two normal individuals on February 22. Identical technics were used. These control tests both showed a much less marked rise, with a more rapid fall and ultimate blood sugar level about the same as the patient's, as is noted in the accompanying table (Table 2).

TABLE 2

INTRAVENOUS SUGAR TOLERANCE TESTS ON PATIENT A. N. AND CONTROL SUBJECTS

Date	Intervals							
	Fasting	15 Min	30 Min.	45 Min.	60 Min.	90 Min.	135 Min.	
Feb. 17, 1933.....	71	408	376	....	65	47	59	Patient A. N.
Feb. 22, 1933.....	85	230	85	94	52	51	60	Control No. 1
Feb 22, 1933.....	79	232	162	109	62	65	68	Control No. 2

In order to determine whether an adrenalin insufficiency allowing a relative or actual hyperinsulinism to occur might be partially responsible for the greatly increased tolerance, it was decided to give adrenalin at the time of a sugar tolerance test. This was carried out on February 28. The patient was subjected to the usual sugar tolerance test except that an ampoule of Parke Davis adrenalin was given by hypodermic after the fasting specimen of blood was withdrawn. The blood sugar values were as follows: fasting specimen, 66 mgm./100 cc.; 50-minute specimen, 266 mgm.; one-hour specimen, 298 mgm.; two-hour specimen, 299 mgm./100 cc. The patient was discharged on March 3, 1933.

SUMMARY

A case of Addison's disease with marked increase in carbohydrate tolerance is presented. The initial sugar tolerance curves were inverted. The reaction to a combined adrenalin-sugar injection suggested that the

increased tolerance was associated with a relative hyperinsulinism resulting from degenerative processes interfering with normal adrenalin production. Clinical evidence indicated medullary as well as cortical involvement of the suprarenal glands.

The author wishes to acknowledge his great appreciation of the assistance rendered by Dr. Sulayman Mufarrij in the studies made on this case.

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A POSSIBLE CAUSE OF UTERINE FIBROIDS

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Uterine fibroids, the most common pelvic neoplasm, have commanded the interest of all gynecologists. Their treatment, both by operation and by radium, has been thoroughly discussed in current medical literature, yet little has been written concerning their etiology. With the additions to our knowledge about the ovarian and anterior pituitary hormones, glandular dysfunction is becoming more and more prominent as a possible cause of fibroids. This paper offers a series of 275 cases of fibroids, the analysis of which evidences a possible etiological relationship between continuous oestrin stimulation from the ovary and the formation of hyperplasia of the endometrium and fibromyomatous growths of the myometrium.

The relative frequency of fibroids in negroes has suggested in the past the influence of race as a possible etiological factor. This fact is mentioned because in our Southern hospitals, where the admission of white and colored women is about equal, a preponderance of these tumors is noted in the colored women, in a ratio, roughly, of 10 to 1. Bulloch describes a possible fibroid tendency in the negro as a racial peculiarity, though there is a general impression extant that these growths were unknown among the primitive tribes. Why there should be any relationship between the development of fibroids and the advancing civilization of negro women is difficult to understand. Suffice it to say that scientific data are still wanting to confirm definitely that either heredity or race is a cause.

Another theory concerning their etiology is that of Sampson, who suggests that fibroids may be due to local hyperplasia of the uterine muscle cells, caused by the stimulus of menstrual blood which has reached them by retrograde current. He explains the absence of these tumors in the cervix and tubes on the ground that these structures do not menstruate. Again, sterility is undoubtedly a factor, since it is found to be at least three times as prevalent in association with fibroids as it is under normal conditions (Lynch). That fibroids occur most frequently in virgins and in absolutely, or relatively sterile, women is an accepted fact. One child sterility has been noted in 50 per cent of married colored women with fibroids studied at Charity Hospital (New Orleans). A possible explanation of this fact is that uterine muscle is primarily designed to respond to pregnancy, and should no pregnancy intervene, the uterus is stimulated by a less powerful influence and hypertrophies in an abnormal fashion, resulting in the development of fibroids (Cullen). This theory, however,

does not offer an explanation of their presence in the parous woman, nor does it explain their rapid growth when associated with pregnancy. The essential problem is whether sterility is the cause of fibroids, or fibroids the cause of sterility.

Since the incidence of uterine fibromyomas is confined generally to woman's functional years, ovarian activity in some fashion is undoubtedly an etiological factor. Women with a glandular dysfunction have a tendency to develop fibroids around the age of thirty-five. Oftentimes these women have irregular and painful menstruation in their early twenties; upon curetting this type of patient, hyperplasia of the endometrium is frequently encountered, and even though no fibroids can be detected clinically at this operation, during the next five or ten years fibroids often develop. It is interesting to find that Polak has a similar clinical impression. He comments that the unbalanced glandular type of patient has a marked tendency to develop fibroids. Likewise, Lynch has noted thyroid envolvement in 15 per cent of patients with fibroids. These general clinical impressions and observations have only experience as a foundation, yet their existence evidences a trend of thought along the line of ovarian hormone influence on the uterus.

That hyperplasia of the endometrium is the result of follicular hormone stimulation, unopposed by any corpus luteum influence, and with a possible anterior lobe pituitary association in the background, has been definitely proven by Schroeder and Meyer in Germany, Shaw in England, and Novak, Fluhmann, Graves and Burch in America. In general this hypothesis as the cause of endometrial hyperplasia is attested by the following facts: (1) it is observed during woman's menstrual life, and occurs mainly at the two extremes when the ovarian cycle tends not to follow its normal rhythm; (2) uterine hemorrhage is checked by removing all ovarian tissue, or destroying its function by x-ray; (3) curettage gives only temporary relief, suggesting that the underlying disorder has not been reached; (4) oestrin has been proven experimentally to stimulate endometrial hypertrophy, and the histological picture resulting from this stimulation is similar to that found in hyperplasia of the endometrium; (5) it is found after the menopause resulting from granulosa cell tumors which give rise to excess oestrin activity; (6) the absence of the corpus luteum precludes any progestin stimulation; and finally (7) no evidence of an inflammatory origin is to be found, since it occurs in very young girls.

If it can be accepted that ovarian follicle stimulation is the cause of hyperplasia of the endometrium, it is logical that the reverse ought to hold —namely, when endometrial hyperplasia is found in curettments, the diagnosis of ovarian follicle cysts can be assumed, even though the abdomen is not opened.

Since the uterus as a whole is involved in the reproductive process, the action of oestrin should not be limited solely to the endometrium; the

myometrium should also be involved, and all the more so when the oestrin stimulation is abnormal. It is this fact that I wish to present as a possible cause of uterine fibroids. The endometrium is in a constant state of change, and it is easy to see that any abnormal stimulation to the uterus should first be manifested in the endometrium. The growth of fibroids, however, is not noticeably rapid, and consequently any stimulation to the myometrium which causes fibroids would have to persist over a rather lengthy period. My assumption is that the unopposed action of oestrin on the uterus results first in immediate endometrial changes, characterized by hyperplasia, and second, in more latent myometrial disease, in the nature of fibromyomatous growths.

Using the above hypothesis as a basis, the cases of 26 subjects of hyperplasia of the endometrium, operated on and diagnosed as such, and on whom a second operation for multiple fibroids was performed after an approximate interval of four years and four months, are analyzed. In addition, 124 cases of fibromyomas in white women and 125 in colored women, diagnosed microscopically, are offered with the associated ovarian and endometrial findings, as presenting added evidence in support of a cause and effect relationship between hyper-oestrin stimulation, hyperplasia of the endometrium, and fibromyomatous growths of the myometrium.

In the accompanying tables, which are not reviewed in detail, rather striking incidents were noted. The symptoms between the first and second operations offer an interesting comparison, the outstanding feature of which is an increase of complaints. Both bleeding and pain increased after the first operation, while an abdominal mass appeared in five instances. In every case the microscopic diagnosis of the curettments from the first operation was hyperplasia of the endometrium. At the second operation, multiple fibroids were observed (100 per cent) even though no such tumors were noted clinically at the time of the first operation, which involved abdominal exploration in 13, or 50 per cent of the cases. In addition to the fibroid growths, the endometrium was hyperplastic in 24, or 92.3 per cent of the cases; in two instances in which hyperplasia of the endometrium was not noted, a developing corpus luteum was found in one of the ovaries.

Unless both ovaries, or the total ovarian tissue, are studied in their entirety it is unwise to draw conclusions concerning the presence or absence of the corpus luteum, since its absence is so importantly related to hyperplasia of the endometrium. In 18 cases, or 69.2 per cent, both ovaries, or the total remaining ovarian tissue, were studied, while in 8 cases only one ovary was available for microscopic section. Follicle cysts of the ovaries were present in all 26 cases, including those in which the corpora lutea were found. Salpingitis, or adhesions from previous operations, or endometrial transplants, were found in 25 cases, or 96.1 per cent. This tube-ovarian infection is offered as a possible etiological factor in

TABLE I

NUMBER OF PATIENTS—26

Symptoms at First Operation		Symptoms at Second Operation	
Menorrhagia	13	Menorrhagia	16
Metrorrhagia	6	Metrorrhagia	3
Dysmenorrhoea	7	Dysmenorrhoea	9
		Abdominal Mass	5
		Nervous, Irritable	5
		Amenorrhoea after Radium	2*
		No effect from Radium	4
		Pregnancy after "D. and C."	2

*Lasted 3 and 6 months, respectively.

Type of First Operation		
Dilatation and Curettage	29*	
Application of Radium	6§	
Suspension of Uterus	3	
Appendectomy	4	13 (50%)
Unilateral Salpingo-oophorectomy	5	
Bilateral Salpingectomy	1	

*One patient had 2 "D. and C's."; another 3.
§Number of hours undetermined.

Condition of Ovaries at First Operation	
Diagnosed microscopically as Cystic	5
Diagnosed operatively as Cystic	5
Not mentioned at operation	3

Curettings	
Hyperplasia	29
Abundant	4
Moderate amount	8
Small	5
Polypoid	4
Amount not mentioned	8

Time Interval Between Operations
Longest—13 years, 2 months.
Average—4 years, 4 months.
Shortest—1 year, 2 months.

Type of Second Operation	
Hysterectomy	26
Bilateral Salpingo-oophorectomy	13
Removal of all Ovarian Tissue	5
Unilateral Salpingo-oophorectomy	8

Condition of Myometrium	
Hyperplastic	6
Fibromyomas, Multiple	26
Fibrotic	5
Adenomyomatous	1
Malignant Degeneration	1
Normal	11
Metritis	1
Bicornuate Uterus	1

Condition of Endometrium	
Hyperplastic	24
Pre-menstrual	2

Ovaries		
Both Ovaries examined microscopically	13	
All Ovarian Tissue examined microscopically	5	18 (69.2%)
Only one Ovary examined microscopically	8	

Condition of Ovaries at Second Operation	
Follicle Cysts	26
Corpus Luteum	
Mature	2
Degenerating	5
Absent	19

Miscellaneous Findings		
Salpingo-oophoritis	11	
Ovarian adhesions	14	25 (96.1%)
Endometrial transplants to Ovary	7	(27%)

follicle cyst formation, either through an inherent ovarian defect, or because of a thickening of the ovarian capsule.

TABLE II

NUMBER OF PATIENTS—124

Type of Operation		
Hysterectomy	124	
Bilateral Salpingo-oophorectomy	33	
Unilateral Salpingo-oophorectomy	41	
Ovaries left in situ	50	
Condition of Endometrium		
Hyperplasia	124	
Carcinomatous	1	
Condition of Myometrium		
Multiple fibroids	124	
Hyperplastic	32	
Fibrotic	27	
Adenomyomatous	5	
Carcinomatous	1	
Sclerotic vessels	5	
Metritis	6	
Endometrial transplants	3	
Normal	53	
Condition of Ovaries		
Follicle Cysts (microscopically)	83	
Follicle Cysts (operatively)	41	
Corpus Luteum		
Absent	114	
Degenerating	10	
Dermoid Cyst	1	
Carcinomatous	1	
Miscellaneous Findings		
Salpingo-oophoritis	121	(97.6%)
Ovarian adhesions	48	
Endometriai transplants to ovary	41	(30.2%)

In the second group of 124 white patients with fibroids, follicle cysts were found in every instance, while no mature corpus luteum was noted. Likewise, hyperplasia of the endometrium was diagnosed microscopically in every case.

TABLE III

NUMBER OF PATIENTS—125 (COLORED)

Type of Operation		
Hysterectomy	125	
Bilateral Salpingo-oophorectomy	85	
Unilateral Salpingo-oophorectomy	30	
Ovaries left in situ	10	
Condition of Myometrium		
Multiple fibroids	125	
Hypertrophied	92	
Fibrotic	25	
Not mentioned	8	
Condition of Ovaries		
Follicle cysts	121	(96.8%)
Both ovaries, or total ovarian tissue studied	85	(68%)
One ovary studied	30	
Corpus leutum degenerating	4	
Dermoid cyst	1	
Condition of Tubes		
Salpingitis	125	(100%)
Wassermann positive	28	(22.4%)

In the group of 125 cases of colored women with fibroids, again ovarian follicle cysts were noted in 96.8 per cent, but due to the inadequacy of the records, the microscopic study of the endometrium was not

available in a sufficient number of cases to justify its inclusion. Attention is called to the high (100 per cent) incidence of salpingitis associated with fibroids in the colored women. Alsobrook likewise noted this condition—99.1 per cent, in 1000 cases of fibroids in the same race. In another communication I have endeavored to show that this infection is a disturbing influence on normal ovarian function, and that it is the probable cause of the ovarian disorder so often associated with it.

SUMMARY

The evidence advanced by such competent observers as Schroeder, Meyer, Shaw, Novak, Graves and Fluhmann, is certainly sufficient to warrant the acceptance of a cause and effect relationship between oestrin stimulation and hyperplasia of the endometrium, but I believe that the action of oestrin is not limited solely to the endometrial layer, and that the myometrium is also involved. The 275 cases of fibroids which are presented, associated with ovarian follicle cyst formation, and necessarily hyperoestrin stimulation, offer definite evidence of an etiological relationship between fibromyomatous changes in the myometrium from ovarian follicle stimulation, provided the latter is prolonged sufficiently.

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CLINICAL EVALUATION OF COMBINED PROLAN AND ANTERIOR PITUITARY THERAPY*

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Intensive experimental and clinical observations during the past decade have definitely established that sex function and body growth depend totally upon stimuli from the anterior lobe of the hypophysis, and that the latter, to a degree, also stimulates the adrenals, thyroid and possibly other glands of internal secretion.

In the absence of adequate quantities of the gonad-stimulating hormone in pituitary extracts for therapeutic use, the discovery in 1928 by Aschheim and Zondek (1) of a substance in the urine of pregnant women capable of evoking an ovarian response in the rodent qualitatively identical with that of implants and extracts of anterior lobe tissue met with the fondest hope that a therapeutic agent for functional menstrual disorders was at last available in sufficient quantity to meet the needs of the medical profession. Disappointment followed the realization that only 10 per cent of amenorrheic women respond to treatment with the product when it is employed as the sole agent. Functional uterine bleeding, if due to pituitary deficiency, responds quite favorably to prolan treatment. The difference in response of the two conditions (amenorrhea and functional uterine bleeding) to prolan treatment was at first explained on the basis that the product is purely luteinizing in effect and, therefore, incapable of stimulating the inactive follicles of amenorrheic women to growth and function preparatory to luteinization. Without entering into discussion on the unity or duality of the anterior pituitary sex hormone, we may state without reservation that prolan, which, as will be seen later, is not identical with the former, is capable of evoking both phases of the ovarian cycle in most experimental animals. A notable exception is the immature macacus monkey in which prolan produces no ovarian response (Engle, 2).

The relative ineffectiveness of prolan in the treatment of amenorrhea and oligomenorrhea may be explained theoretically on the basis of variability of species response, namely, that, in the human, the product is incapable of evoking growth of the primordial follicle (oestrin phase), though its luteinizing effect, as shown by Zondek (3), is considerable. This deduction is by analogy supported by the observations of Saiki (4) and Hisaw (5) that transplants and extracts of anterior lobe tissue evoke in the immature rhesus monkey only the follicular phase of the ovarian

*The term "prolan," herein employed, refers to the anterior pituitary-like substance obtained from the urine of pregnant women, commercially supplied under various names, such as follutein, antuitrin-s, etc.

cycle and consequent bleeding from an interval endometrium; luteinization is either slight or totally absent.

A more plausible explanation of the relative ineffectiveness of prolan in the treatment of amenorrhea and oligomenorrhea of pituitary origin is that these conditions are expressions of a severer form of pituitary deficiency than is functional uterine bleeding, requiring, as it were, a greater stimulus than that which prolan can produce. The limitation of prolan in its effect on the animal gonads was definitely demonstrated by Evans (6) and Leonard (7).

THE IDENTITY OF PROLAN

From the therapeutical standpoint, the identity of prolan is a matter of the utmost importance. If it were identical with the pituitary sex

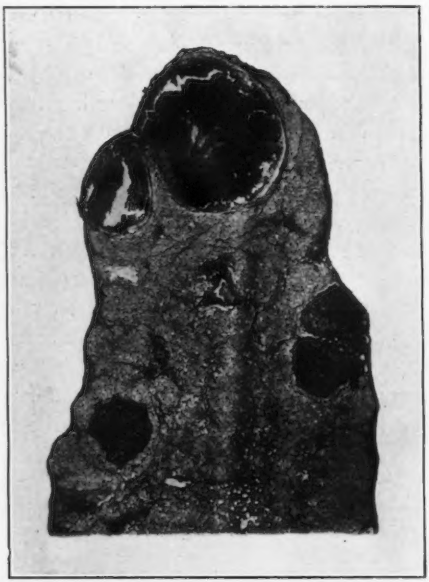

Figure I. Part of ovary of isolated mature rabbit after 3 intravenous injections of prolan. Note the hemorrhagic follicles (low power).

hormone, its effect in the treatment of pituitary deficiencies would be purely substitutive and not curative, since no endocrine gland is self-stimulative or autokinetic.

Engle (8) was the first to question the identity of prolan and pituitary hormone because injections of prolan, unlike daily pituitary implants, often produce corpora lutea atretica and follicular hemorrhage. He failed, however, to take into account the fact that the rate of absorption of the hormone from pituitary implants is slow and continuous, whereas, absorption of the hormone from injections of pregnancy urine is rapid and inter-

mittent. A striking illustration of the importance of the rate of absorption of the hormone in relation to ovarian response is the severe reaction of the rabbit's ovaries (many large, hemorrhagic follicles which do not rupture) to intravenous injections of either prolan or anterior pituitary extract in contrast with the natural transformation of the ovarian follicles into normal corpora lutea when either of the two hormones is administered daily by the hypodermic route (Figs. I and II). It is now definitely established that the qualitative ovarian response of the immature rodent and rabbit to pituitary extract and to prolan is identical and that differences recorded by various observers are due to variability in dosage, mode of administration and species-susceptibility.

Figure II. Part of ovary of isolated mature rabbit after 3 hypodermic injections of prolan. Note the absence of hemorrhagic follicles and the presence of a well-developed corpus luteum (low power).

Biological dissimilarity between prolan and anterior pituitary sex hormone is shown by the following observations:

(1) The limited effectiveness of prolan. No matter how large a quantity of prolan is administered to an infantile rat in the course of four days, the maximum increase in ovarian weight is far below that obtained with adequate amounts of anterior pituitary extract (Evans, 6, 9). Leonard (7, 10) has likewise shown that, in the rabbit, the ovulating dose of anterior pituitary extract is very much less than that of prolan (1:4) when the potency of the two substances is standardized on immature female rats. It is thus apparent that, while the qualitative effect of the

two substances on the ovaries of immature rodents and isolated adult rabbits is identical, quantitatively the effect varies considerably.

(2) The hypophyses of castrated adult rats injected with the anterior pituitary-like substance obtained from the human placenta contain larger quantities of the gonad-stimulating hormone than the hypophyses of untreated castrated rodents (Klinger, 11). Pituitary implants, on the other hand, do not increase hypophyseal potency (Philipp, 12; Ehrhardt, 13).

(3) Prolan and pituitary extracts when given simultaneously are synergistic (Evans, 6; Leonard, 16). This is in contrast to the marked nullifying effect which the growth hormone exerts upon the pituitary sex hormone when the latter two are administered simultaneously (Evans, 14; Leonard, 15).

(4) Prolan, unlike gonadotropic pituitary extract, produces no follicular growth and consequent endometrial development in the immature macacus monkey (Engle, 2; Diddle, 17).

(5) More conclusive evidence that prolan is not identical with the anterior pituitary sex hormone is the relative ineffectiveness of the usual quantity of prolan to produce an ovarian response in hypophysectomized immature animals (Reichert, 18). This is in striking contrast to the ease with which the ovaries of hypophysectomized animals respond to implants of pituitary tissue and extracts thereof. With the use of enormous doses of prolan (400 rat units daily), Reichert (18) did obtain an ovarian response in hypophysectomized rats. Smith and Leonard (19), on the other hand, while conceding the relative ineffectiveness of prolan in hypophysectomized animals, were able to induce with smaller doses (40 to 50 rat units) a modified luteinization of atretic follicles and even oestrus in hypophysectomized rats. They observed, however, no follicular growth in the treated animals. These discordant findings require further study. The possibility that such large doses of prolan contain as an admixture variable quantities of the true pituitary sex hormone, which is highly effective in hypophysectomized rodents, must be borne in mind.

While the above-mentioned experimental observations and others cited in the following paragraphs seem to show conclusively that prolan is not identical with the pituitary sex hormone, Friedman's (20, 21) observations are somewhat contrary to this conclusion. He was able to produce unilateral corpora lutea and, in some instances, progestational endometria in isolated rabbits by direct unilateral intrafollicular injections of antuitrin-s or follutein. The absence of any discernible changes in the corresponding untreated ovary is suggestive that even minute doses can produce luteinization without the aid of the anterior lobe of the hypophysis. If Friedman were able to obtain the same results in hypophysectomized animals, the ability of small doses of prolan to evoke an ovarian response without the aid of the anterior pituitary lobe would not be questioned.

MODE OF ACTION OF PROLAN

The relative ineffectiveness of prolan in hypophysectomized animals naturally led to the conclusion that in the normal animal it either stimulates the pituitary sex cells to increased activity or converts an inactive substance (prohormone) within the hypophysis into an active sex hormone. The observations of Berblinger (22), Baniecki (23) and Lehmann (24) that the hypophysis of rabbits, guinea pigs and rats injected with placental extracts showed definite stimulative changes (pregnancy reaction) strongly supports the view that prolan has a stimulative effect on the anterior pituitary lobe. That the oestrin-content of the placental extracts, employed by these investigators, was not responsible for the reac-

Figure III. Control ovary of an infantile rabbit.

tions noted in the hypophyses of the treated animals is evident by the observations of Kunde (25) that the administration of large doses of oestrin in immature dogs results in atrophy rather than increased weight of the anterior pituitary lobe. Likewise, a decrease in pituitary potency of oestrin-treated rats was noted by Leonard (26) and others. The hypophyseal pregnancy changes evoked by prolan cannot be induced by means of implants of anterior lobe tissue (Philipp, 12; Ehrhardt, 13). In the human, hypophyseal pregnancy changes apparently due to prolan stimulation were found by Rössler (27), Novak (28) and Zondek (29) in cases of chorionepithelioma—a condition characterized by the presence of immense quantities of prolan. These experimental and clinical observations

seem to indicate that the placental hormone, prolan, stimulates the sex cells of the hypophysis.

The experimental observations of Evans (6, 9) and Leonard (15), though not contradicting the foregoing conclusion, are suggestive of the ability of prolan to convert an inactive hypophyseal substance (prohormone) into an active sex hormone.

Evans and his co-workers observed that the combination of prolan and hypophyseal extracts, rich in the growth-promoting hormone and relatively free from the gonadotropic hormone, stimulates development of immature rat ovaries (gauged by weight and microscopic appearance) to

Figure IV. Ovary of infantile rabit injected hypodermically with 35 c.c. of pituitary extract over a period of five days. The product was prepared by the Van Dyke and Wallen-Lawrence method, and is said to be free from the gonad-stimulating hormone. Compare with Figure III and note evidence of maturation, due to the presence in the extract of small quantities of the gonad-stimulating hormone.

a far greater degree than could be expected by any additive effect resulting from the use of the two constituents individually. They also found that the administration of constant amounts of prolan with decreasing quantities of the hypophyseal extract resulted in rapid diminution in the ovarian response, and conversely that a moderate decrease in the prolan component did not materially affect ovarian activation. They (6) therefore came to the following conclusions: "The gonad-stimulating hormone is present in the hypophysis in an inactive state. The active substance is formed from this prohormone by the activator. This activator is found in the most concentrated form as prolan in the urine of pregnant women.

It may also be present in the hypophysis itself, even in the infantile hypophysis. In the normal infantile animals its [prolan] effect is limited by the small amount of the prohormone present.''

Leonard (15) and Fevold (30), on the other hand, employing a combination of prolan and sheeps' pituitary extract, free from the growth-promoting hormone and rich in the gonad-stimulating principle, likewise obtained ovarian weights in immature rats averaging 142 per cent greater than the sum of the increased weights produced by each component individually. Their observations led to the conclusion that the gonad-stimulating hormone is enhanced in its activity by the addition of prolan and that the growth-promoting hormone plays no rôle in this reaction.

Figure V. Ovary of infantile rat, after injection of 6 c.c. of the presumably pure growth hormone. Note the corpora lutea, indicating that the extract contained minute quantities of the gonad-stimulating hormone as an admixture.

Whether prolan converts the growth-promoting principle into an active gonad-stimulating hormone, as originally claimed by Evans (9) or merely enhances the activity of the gonadotropic hormone, as claimed by Leonard (15), became a pertinent question since the supply of the latter to be used in combination with prolan is too meager for clinical use.

Realizing the practical importance of this problem, we employed both products individually and in combination with prolan on immature rats and rabbits as a preliminary to the clinical use of combined injections of prolan and anterior pituitary extracts.

That the so-called growth hormone, prepared by the method of Van Dyke and Wallen-Lawrence, contains small quantities of the gonad-stimulating hormone was evident from the observation of Leonard (16) that one-half cc. of the product is capable of causing ovulation in the oestrous rabbit (postpartum or otherwise). He found, however, that even larger quantities of the hormone failed to produce maturity effects in infantile rodents. This suggested the possibility that the anterior lobe of the hypophysis produces an individual ovulation-inducing hormone.

Our experimental observations, however, show that the so-called growth hormone, when employed in adequate quantities, produces follicular growth, ovulation and luteinization in immature rabbits and rodents as well as ovulation and luteinization in the isolated mature rabbit (Figs. 3, 4 and 5). We frequently found as much as one mouse unit of the gonad-stimulating hormone in 3 cc. of the growth-promoting extract.

The finding of variable quantities of the gonad-stimulating hormone in the growth-promoting pituitary extract undermined Evans' (6) theory that the growth hormone is converted into an active sex hormone by the addition of prolan and was somewhat supportive of Leonard's theory that the sex hormone component of pituitary extracts is enhanced in its activity by the addition of prolan. The possibility that an unknown factor present in both pituitary extracts is the responsible agent was still present. In the light of Evans' very recent findings (31), this possibility apparently materialized.

We were able to confirm the findings of Evans (6) on rats and of Leonard (7) on rabbits that the combination of anterior pituitary extract and prolan produces a much greater ovarian response than either of the two products employed individually (see Tables I and II).

TABLE I

EFFECT ON IMMATURE RATS OF THE COMBINATION OF A HALF OR LESS OF THE EFFECTIVE DOSES OF PROLAN AND THE GROWTH-PROMOTING PITUITARY EXTRACT CONTAINING MINUTE QUANTITIES OF THE GONADOTROPIC HORMONE

Prolan			Pituitary Extract		Combination		
Preparation Used	Total Dose	Weight of Ovaries	Total Dose	Weight of Ovaries	Total Dose of Prolan	Total Dose of Pituitary Extract	Weight of Ovaries
	c.c.	mg.	c.c.	mg.	c.c.	c.c.	mg.
Dilute follutein.....	6	29	24	21	2.	9.	60
Dilute follutein.....	6	41	24	22	2.	9.	80
Dilute follutein.....	6	55	24	17	2.	9.	72
Specimen of diluted pregnancy urine.....	21	26	21	17	10.5	10.5	60
Specimen of diluted pregnancy urine.....	21	24	21	21	10.5	10.5	48

TABLE II

THE EFFECT OF THE COMBINATION OF HYPODERMIC INJECTIONS OF HYPOPHYSEAL PREPARATIONS AND PROLAN ON THE OVARIES OF IMMATURE RABBITS

Hypophyseal Component			Pregnancy Urine		Combination		
Preparation	Total Dose	Weight of Ovaries	Total Dose	Weight of Ovaries	Total Dose Pregnancy Urine	Total Dose Pituitary Extract	Weight of Ovaries
	c.c.	mg.	c.c.	mg.	c.c.	c.c.	mg.
Growth-promoting extract.	42	16	20	90	10	30	167
Growth-promoting extract.	54	15	2½	22	2½	27	60
Growth-promoting extract.	30	29	2½	19	4½	27	75
Gonado-tropic extract.....	10	46	20	68	5	10	212
Gonado-tropic extract.....	10	39	20	90	10	10	245

The growth-promoting extract used in our experimental and clinical investigations was made in the Biological Laboratories of E. R. Squibb & Sons by a modification of the Van Dyke and Wallen-Lawrence method of preparing the growth hormone from the anterior lobes of cattle. The material is standardized by the increase in weight following daily injections of 1 cc. of the product into plateaued female rats weighing 250 to 300 grams. In such animals, under these conditions, it causes a 15 per cent increase in body weight in the course of two weeks. This product contains variable quantities of the thyroid-stimulating hormone, determined by the increase in oxygen consumption of the guinea pig following subcutaneous injections. It also contains, as previously mentioned, minute quantities of the gonad-stimulating hormone.

The sex hormone, relatively free from growth hormone, obtained from sheep's pituitaries, was also prepared in the Biological Laboratories of E. R. Squibb & Sons and generously given to us in sufficient quantities to carry out comparative laboratory studies, but insufficient in quantity for clinical use.

We obtained approximately the same results irrespective of which of the two pituitary extracts was used in combination with prolan. If the activated principle were the pituitary sex hormone component, the use of a concentrated solution of the latter in combination with prolan should have given us better results than with the use of the growth-stimulating product which contains only minute quantities of the gonad-stimulating hormone. Nor did Leonard who employed a comparatively concentrated solution of the pituitary sex hormone in his experimental work on rats obtain greater ovarian weights than Evans who employed pituitary extracts relatively free from sex hormone. These observations strongly suggested that it is neither the growth hormone nor the sex hormone that is activated by prolan but rather an unknown factor present in the preparations employed by both groups of investigators.

We came to this conclusion at the very beginning (August, 1932) of our experimental and clinical work with combined injections of prolan and pituitary extracts. The recent publication of Evans and his co-workers

(31) establishes beyond doubt the presence of a thus far unknown principle in pituitary extracts which, when employed individually, produces no gonadotropic nor growth effects but when used in combination with prolan produces ovarian stimulation far greater than prolan alone can produce. Moreover, they finally obtained a growth-promoting extract which possesses no synergism when employed with prolan, thus reversing their former position that the growth hormone is the activated principle of pituitary extracts.

CLINICAL STUDIES

In order to determine clinically the advantage of employing the combination of anterior pituitary extract and prolan in the treatment of amenorrhea, oligomenorrhea and hypomenorrhea, statistical data of results obtained with the use of prolan alone must be taken as a standard for comparison. Since those who reported on the use of prolan in these conditions made no attempt to restrict treatment to verified cases of pituitary deficiency, it was necessary for statistical comparison that we likewise treat amenorrheas and hypomenorrheas as if they were clinical entities, without regard to the gland primarily responsible for the menstrual disorder. We naturally eliminated those of a non-endocrine nature.

A critical survey of the literature of prolan treatment of menstrual deficiencies and our personal experience (Mazer, 32) show that cures are obtained in only 1 of 10 patients systematically injected with the product, if the term "cured" is restricted to those whose menstrual periodicity and normal flow were restored for a period of no less than six months. The induction of an occasional flow cannot be taken as a criterion of cure. To avoid misunderstanding, we hasten to reiterate that these figures refer to menstrual deficiencies and not to functional uterine bleeding of adolescence and maturity wherein the administration of prolan (follutein or antuitrin-s) produces good results. Another confusing factor in evaluating reported results with prolan treatment is the simultaneous employment of other agents which may have largely contributed to the beneficial results.

The 50 patients with menstrual deficiencies subjected to this clinical study received three weekly injections of 4 cc. of pituitary extract and 30 to 40 rat units of prolan. The latter was in the form of a crude product prepared and standardized in our laboratory as described by one of us (Mazer, 32). None received fewer than 20 injections; most of them received 30 injections; a few were given as many as 60 treatments without ill effects. In three patients, not included in this study, we had to discontinue the injections at the very beginning because of transient local and constitutional reactions.

Classifying this group of 50 patients according to the degree of menstrual deficiency, we find that 27 had periods of amenorrhea varying from 4 to 12 months; 14 menstruated at intervals of 6 to 14 weeks; nine menstruated regularly but very scantily (Table III).

TABLE III

RESULT OF TREATMENT OF MENSTRUAL DEFICIENCIES WITH COMBINED INJECTIONS OF ANTERIOR PITUITARY EXTRACT AND PROLAN

	Amenorrhea (Intervals of 4 to 12 months)			Oligomenorrhea (Intervals of 6 to 14 Weeks)			Hypomenorrhea (Intervals normal· Flow Very Scanty)	
Apparent Cause	Regular Periods for 6 or More Months	Temporary Relief	Not Improved	Regular Periods for 6 or 9 Months	Temporary Relief	Not Improved	Increased Flow	No Increase in Flow
Pituitary deficiency, 24 cases	9	2	5	3	1	1	1	2
Primary ovarian, 13 cases	None	None	6	1	1	3	None	2
Unclassified, 13 cases	3	None	2	2	1	1	None	4
Total	12	2	13	6	3	5	1	8

Only 19 of the entire group of 50 responded to the injections in the form of six or more menstrual flows at regular intervals and fair quantity. A few menstruated while under treatment but failed to continue after treatment was withdrawn.

Only one of the nine women suffering from hypomenorrhea responded to the treatment. It is our experience that hypomenorrhea is more resistant to any form of treatment than secondary amenorrhea.

An appreciable enlargement of the uterus was noted in only four of the group of 19 that responded to the treatment.

Classification of this group of 50 patients suffering from menstrual deficiencies according to the particular gland primarily responsible for the condition shows that 24 were primarily of pituitary origin; that 13 were suffering from primary ovarian failure due to developmental defects; and that 13 did not lend themselves to classification. Subjects of definite thyroid deficiency were not included in this study.

The diagnosis of pituitary deficiency was based on the characteristic regional adiposities, the presence of variable degrees of hypertrichosis, stability of the autonomic nervous system, the absence of dysmenorrhea and fatigue, the frequent presence of a high sugar tolerance and the absence of a demonstrable quantity of pituitary sex hormone in 100 cc. of the morning urine 10 or 12 days after a chance flow.

The diagnosis of primary ovarian failure was based on the superlatively feminine appearance and demeanor of the patient, instability of the autonomic nervous system, the presence of visceroptosis together with spasticity of the colon, the frequent association of primary dysmenorrhea, underweight and marked fatigue. In some an excess of the anterior pituitary sex hormone was demonstrable, both in the blood and urine.

Evident genital hypoplasia was present in the majority of the three groups of patients.

The 24 patients presenting definite stigmas of pituitary deficiency responded best to the combined injections of pituitary extract and prolan;

13 of the 24 thus far menstruated at regular intervals for six or more months; three showed some improvement; the remaining nine showed no improvement. Among the latter is a subject having Simmond's disease. She shows a marked gain in weight and improvement in the skin lesions but thus far has failed to menstruate.

Of the 13 women classified as suffering from primary ovarian failure, only one responded to the treatment. In the unclassified group of 13, five responded to the treatment.

Seven regularly menstruating women suffering from severe primary dysmenorrhea were given from 20 to 30 injections. Only one of these seven was relieved of the condition.

Since dysmenorrhea rarely accompanies pituitary deficiencies, its failure to respond to pituitary treatment is understandable.

CONCLUSIONS AND SUMMARY

Studies now available in the literature indicate that prolan is apparently a placental hormone, not identical with the pituitary sex hormone; that prolan probably stimulates the gonadotropic cells of the hypophysis to a moderate degree; that the anterior lobe of the hypophysis apparently produces a prohormone which, in itself, possesses no gonadotropic properties but is readily converted into an active sex hormone by prolan; and that this prohormone is neither the growth-promoting principle nor the sex-stimulating hormone of the hypophysis. It is, however, present in both extracts.

In three young rabbits and in three rats injections of pituitary extracts (containing this prohormone) and prolan in combination gave better results than those obtained from either of the two employed individually in groups of similar size.

Fifty women suffering from menstrual deficiencies were injected, thrice weekly, with 4 cc. of pituitary extract and 30 to 40 rat units of prolan for a period of 7 to 12 weeks . Nineteen of the entire group of 50 responded to the injections in the form of six or more menstrual flows at regular intervals and fair quantity. A few others menstruated while under treatment but failed to menstruate after the injections were discontinued.

The best results were obtained in definite pituitary deficiencies. Thirteen of 24 women suffering from this disorder responded favorably to the treatment, whereas only one of 13 women suffering from primary ovarian failure was benefited.

Primary dysmenorrhea was not influenced by injections of pituitary extracts and prolan.

The 15 immature rats employed in this experiment were approximately 17 days old. The average weight of the ovaries of the uninjected controls was 8 mg. The average increase in weight of the ovaries as a result of injections of the growth-promoting extract was 11 mg. The average increase in the weight of the ovaries as a result of injections of diluted

follutein or pregnancy urine was 26 mg. The average increase in the weight of the ovaries with combined injections of one-half or less of each component was 56 mg.

The sample of growth-promoting extract employed in this experiment apparently contained very little, if any, of the gonad-stimulating hormone as evidenced by the total absence of ovarian stimulation and the low ovarian weight after the injection of as much as 54 cc. over a period of five days. When used in combination with pregnancy urine, the ovarian response was far greater than the additive effects of the two employed individually. The 15 rabbits employed in this work were young and weighed no more than 2 pounds each.

We herein express our gratitude to Dr. J. A. Morrell, of the E. R. Squibb & Sons Research Laboratory, for the generous supply of pituitary extracts and for valuable suggestions in the construction of the paper.

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ABSTRACTS

The influence of adrenaline on the diastolic blood pressure in aortic insufficiency and Basedow's disease in analogy to beri-beri (Über den Einfluss des Adrenalins auf den diastolischem Blutdruck bei Aorteninsuffizienz und Morbus Basedowii in Analogie zur Beri-beri-Krankheit). Aalsmer, W. C., Klin. Wchnschr. **11**: 362. 1932.

In previous studies by the method of Korotkow on the blood pressure effects produced by 1 mg. subcutaneous doses of adrenaline in beri-beri, the author found that the maximal pressure was raised only temporarily and that the minimal pressure decreased so much that it could not be estimated. The decrease in minimal pressure was proportional to the severity of the disease. The pulse rates as well as maximal and minimal pressures were determined before the injections. The same determinations were made every five minutes for one-half hour after injections. In a series of patients suffering from various disease (pneumonia, typhus, etc.) there were no decided effects from the injection of adrenaline. In two cases of icterus in which the maximal and minimal pressures were 85-50 and 100-35, respectively, the minimal pressure fell to zero in 20 minutes in the first case and to zero in 15 minutes in the second case. Similar effects were produced in two cases of insufficiency of the aortic valves and in Basedow's disease. The amount of fall in minimal pressure seems to be proportional to the peripheral circulatory disturbance.—E. L.

Demonstration of liver contractions by adrenaline (L'épreuve d'hépato-rétraction à l'adrénaline). Benhamon, E. and R. Marchioni, Presse méd. **40**: 1747. 1932. Abst., Endokrinologie, **12**: 133.

X-ray pictures of the livers of fasting patients were taken with uniform technic before the injection of adrenaline and 30 minutes after the injection of 1 mg. of adrenaline to determine the size of the liver. Usually the only preparation necessary was overnight fasting. In normals there is a definite diminution of the liver after adrenaline, the effect is maximum 30 minutes after injection and amounts to about three centimeters. After 80 minutes the liver returns to normal or may even increase in size. In splenectomized patients the contraction is especially marked. The enlarged livers of patients with malaria, cardiac insufficiency, diabetes mellitus, and haemolytic icterus show good contraction if no symptoms of cirrhosis are present. There is no lessening in size of the syphilitic or cirrhotic liver. The phenomenon of liver contraction after adrenaline is comparative to the contraction of the spleen under the same conditions except that the liver is lacking in such widespread contractile elements. It must be assumed that the contraction of the arterioles and capillaries is the basis of this phenomenon and that it is used for the expulsion of the blood from the depot in the liver. Nevertheless all the pathophysiological questions of liver contraction after adrenaline injection have not been completely explained.—Translated by J. Gagnon.

The relationship of epinephrine to muscle and liver glycogen. Bodo, R. C., A. E. Benaglia and M. M. Friedman, Proc. Am. Physiol. Soc. P. 8. 1933.

The work which is reported here was carried out on dogs which were either well-fed or fasted for different lengths of time. Muscle and liver samples were taken at the beginning and at the end of the experiment for glycogen determinations under local anaesthesia after a preliminary injection of a small amount of morphine. During the course of the usual 5-hour experiments, blood samples were taken at hourly intervals for sugar and lactate determinations. The adrenaline was injected intramuscularly in amounts of 1 to 5 cc. for the whole animal as a single injection or repeated as often as five times at hourly intervals. As a result of these injections there occurred a decrease in muscle glycogen irrespective as to whether the animals were fed or fasted, accompanied by an increase in blood lactates. In the liver, however, there occurred an increase in liver glycogen only in the animals fasted for 6-14 days, but a definite decrease in the fed animals following the injection of the same amount of adrenaline.—Authors' Abst.

Carbohydrate versus circulatory theories of cortico-adrenal function. Britton, S. W., Proc. Am. Physiol. Soc. P. 11. 1933.

Measures which ordinarily produce hyperglycemia in normal animals do not do so in adrenalectomized animals. Adrenaline, anesthesia, emotional excitation and other procedures affect the blood sugar levels scarcely at all in adrenal insufficiency. Carbohydrate mobilization is impossible; no glycogen reserves are present in the liver. Cortico-adrenal extract readily restores normal carbohydrate metabolism. Animals dying of adrenal insufficiency show convulsive seizures some hours before death identical in type with those observed in insulin hypoglycemia. Animals dying with severely low blood volume after hemorrhage do not show similar convulsions. Injections of saline and gume-saline solutions readily restore the blood volume of adrenalectomized animals but do not ameliorate the symptoms of insufficiency or prolong life. Glucose injections alleviate the symptoms rapidly and significantly, and increase the survival period. The adrenalectomized animal is an hydrated animal. Abnormal amounts of water are held in the liver and muscle tissues. The blood volume is low, however, and anhydremia is marked. Fluid accessions by the liver and muscle nevertheless more than balance the loss of fluid by the blood in adrenal insufficiency. One of the earliest effects of cortico-adrenal extract is to eliminate fluid from the body by producing diuresis. An understanding has been sought of the chemical conditions and changes in adrenal insufficiency which are antecedent to the altered permeability of the vascular membranes. Breakdown of the normal carbometabolic processes appears to be the primary critical contingency in adrenalectomy.—Author's Abst.

Effects of adrenalectomy and cortico-adrenal extract on reproduction. Britton, S. W. and R. Kline, Proc. Am. Physiol. Soc. P. 12. 1933.

Studies have been made on the albino rat of the effects of adrenalectomy, and of cortico-adrenal extract administration on pregnancy and reproductive ability. Both male and female animals show reduced fertility after both adrenals are removed. Adrenalectomized females may reproduce and rear normal litters. In all cases in which fertility persists after adrenal excision, however, accessory glands are found to be present. In several cases, injections of cortico-adrenal extract have induced labor and terminated pregnancy in unoperated animals.—Author's Abst.

Blood-cellular changes in adrenal insufficiency and the effects of cortico-adrenal extract. Corey, E. L. and S. W. Britton, Am. J. Physiol. **102**: 699. 1932.

A detailed study was made of the blood elements of about 50 animals, including daily erythrocyte determinations and total and differential leucocyte counts in normal, adrenalectomized and cortico-adrenal extract-treated cats, rabbits and rats. Control experiments involved the injection of adrenaline in approximately the concentration found in the extracts used (1:2,000,000), saline and glucose solutions. In some cases (3) splenectomized and splenecto-adrenalectomized cats served as controls. The authors' adrenalectomized control cats survived for an average period of 6½ days. The extract used was made according to a modified Swingle-Pfiffner technique, and was tested for potency on adrenalectomized cats showing symptoms of severe adrenal insufficiency. Erythrocytes (10 cats)—The average normal count for this group was 9,800,000 cells per cu. mm. This average increased to 15,500,000 cells at the time the animals exhibited severe symptoms of adrenal insufficiency. Following extract treatment the count fell to approximately the normal level. Adrenaline (in concentration as above) given in large amounts of fluid failed to influence the cell values to any significant degree. Glucose and saline solutions were likewise ineffective. Leucocytes (total count, 9 cats)—The average normal count was 12,400 cells per cu. mm. This average fell to 7,000 cells in severe adrenal insufficiency and following extract administration returned to approximately the normal level, coincidentally with the return of the animals to normal condition. Leucocytes (differential count, 9 cats)—The normal percentages of neutrophiles and leucocytes for this group averaged 63 and 32, respectively. Following adrenalectomy these values were altered to 30 and 64. Following extract treatment, a return to the normal values was observed—neutrophiles, 58%; leucocytes, 36%. Rabbits (6) gave values comparable to those observed in the cat. In the rat, adrenaline appeared to be able to raise

the (previously reduced) neutrophile count, but not as markedly as did the extract. The cell values in splenectomized cats did not differ significantly from those found in normal animals; splenecto-adrenalectomy resulted in reduction in the white count as above, with return to normal following cortico-adrenal extract injection. Adrenaline failed to produce any marked shifts in the leucocytes of these animals. The rise in red cell concentration noted above is possibly attributable to extensive shifts in the water balance of the organism. The leucocytic changes indicate the possibility of a neutrophilogenic failure in the adrenalectomized animal with an apparent related lymphocytosis. The possible involvement of the bone marrow and other tissues in adrenal insufficiency is thus indicated. The possibility that the neutrophilopenia of adrenal insufficiency is related to the clinical condition of "agranulocytosis" may be considered.—E. L. Corey.

Diagnosis and treatment of Addison's disease. Harrop, G., A. Weinstein, L. J. Soffer and J. H. Trescher, J. A. M. A. **100:** 1850. 1932. Abst., A. M. A.

During the past two and a half years the authors treated 13 cases of Addison's disease by means of the suprarenal cortical extract made according to the method of Swingle and Pfiffner. The diagnosis of each of these cases they have regarded as unequivocal. There were seven deaths. The other six patients are now living. All of the seven fatal cases have come to necropsy, and the clinical diagnosis of Addison's disease has in each been proved correct. Four were due to cortical atrophy. The authors believe that the clinical value of injections of the cortical hormone as a routine treatment during the remissions of Addison's disease has not been satisfactorily demonstrated. So far as their experience indicates, however, there is no danger whatever in the use of extract if this seems desirable. They stress the fact that they have never seen any untoward or toxic effects as a result of the treatment by cortical extract, although they have used it in many types of patients, some of whom have received large doses both subcutaneously and intravenously. The authors do not doubt, however, that a faulty preparation may lead to dangerous consequences. The extract has no definite effect on hypotension or on the pigmentation. They are not convinced that it has any effect on nutrition and weight. The chief value of the cortical extract lies in the treatment of the relapse, the symptoms of which they regard as fundamentally those of shock, and due primarily to cortical deficiency. In patients showing such symptoms for longer or shorter periods, injections of the cortical hormone extracts are of definite value and may be of vital importance.

The effect of epinephrine in lipid excretion. Hill, Elsie and A. E. Koehler, J. Biol. Chem. **98:** 185. 1932.

The effect of epinephrine injection in white rats on low fat diet was studied. Epinephrine was injected intraperitoneally or subcutaneously in subglycosuric doses of 0.02 mg. per 100 gm. body weight given three times daily for a period of two to three days. In the first four groups, totaling 27 rats, epinephrine caused an average increase in lipid excreted of 101% on the day following injection. It remained elevated during injections and for as long as three days after cessation of epinephrine administration, then returned to normal. Group five, containing nine rats, had no significant change in total lipid excreted, although the percentage in dried feces increased on the day following epinephrine administration, as did the ratio of lipid excreted to lipid ingested, though not as markedly as in the previous groups.—Hazel Childs.

The hormone of the suprarenal cortex and the genital system (Nebennierenrinden-Hormone und Genitalsystem). Kaplan, S., Endokrinologie, **11:** 321. 1932.

Male and female white rats three weeks of age were injected with five types of extract of the adrenal cortex until they were three months of age, at which time the genital organs were observed microscopically and macroscopically. Macroscopically there was no definite change in the genital organs of either sex. The microscopic changes agreed in general, with those published by Amson, Connor and Corey and Britton. No details are given.—R. A. Phillips.

Relation of adrenal cortex to development of scurvy. Lockwood, J. E., D. G. Hartman and F. A. Hartman, Proc. Soc. Exper. Biol. & Med. **30**: 560. 1933.

Three groups of guinea pigs, 9 or 10 animals in each, were placed on a vitamin C free diet. A group of controls developed severe scurvy. A group with one adrenal gland removed developed a mild scurvy, but more severe than in a group given 0.7 cc. of orange juice per day per animal, and about as severe as in a group given 2 cc. of cortin daily. A group with one adrenal removed and given 0.7 cc. of orange juice per day remained almost free of scurvy. A group with adrenals intact given the same amount of orange juice developed definite signs of scurvy. The authors suggest that cortin aids in the utilization of vitamin C, and that when one adrenal gland is removed the over-compensation in the production of cortin by the remaining gland serves for better utilization of the vitamin C available.—M. O. L.

Experimental production of chronic and sub-acute adrenal insufficiency in dogs and cats. Rogoff, J. M., Proc. Soc. Exper. Biol. & Med. **29**: 1240. 1932.

In dogs and cats successful attempts were made to produce a condition of sub-acute and chronic adrenal insufficiency, comparable with Addison's disease, by subtotal ligations of the adrenal bood vessels. The survival periods ranged from two to 14 months. Phenomena of anorexia, vomiting, asthenia and nervous symptoms appeared, and changes in the blood similar to but less severe than those occurring in adrenalectomized animals.—M. O. L.

Secretion of adrenine in experimental diabetes in dogs (L'adrénalino-sécrétion au cours du diabète expérimental du Chien). La Barre, J. and P. Houssa, Compt. rend. Soc. de biol. **109**: 1133. 1932.

Five depancreatized dogs were given injections of insulin and later of glucose. Adrenine was tested for by the intestinal segment method. As the blood sugar fell, adrenaline secretion increased. When the blood sugar was increased, adrenine secretion decreased.—J. C. D.

The nature of the responses of smooth muscle to adrenin and the augmentor action of cocaine for sympathetic stimuli. Rosenblueth, A. and D. McK. Rioch, Am. J. Physiol. **103**: 681. 1933.

The nictitating membrane of the cat submaximally contracted by adrenine contracts further if the cervical sympathetic is stimulated. Similarly, a further contraction is obtained on injecting adrenine during the submaximal response occasioned by maximal shocks applied to the cervical sympathetic at a rate of about 5 per second. This leads to the conclusion that the responses to adrenine are true contractions, not contractures. Cocaine augments the contractions obtained from nerve stimulation by either single or repetitive shocks, as it augments the responses to adrenine.—Authors' Abst.

The interrelationship between the pituitary gland, the ovaries and the placenta. Collip, J. B., Tr. Roy. Soc. Canad. **26**: 1. 1932.

In this, his Presidential address, Collip offers a brief orienting discussion of the topics mentioned in the title. The article by its very nature does not lend itself to abstracting. Of special interest is his emphasis of the lack of so-called anterior pituitary factors in the blood or urine of pregnant lower animals or in the placenta of other than the higher primates. He dissents from the view that the sex-fraction of anterior pituitary extracts contains separate principles, estrogenic and luteinizing. The belief is expressed that all the sex hormones found in the urine of pregnancy have their origin in the placenta. The probable existence of an "inhibitory principle" in the pituitary is offered as an attractive hypothesis by which a number of apparent contradictions in existing evidence can be harmonized.—R. G. H.

Progress relative to disease of the ductless glands. Rowntree, L. G., Pennsylvania M. J. **36**: 646. 1933.

This is a good condensed review of the subject. Rowntree pays tribute to the pioneers in this field, particularly to the American chemists who have contributed so largely to our knowledge of hormones. If properly applied,

hormonal treatment in the form of substitution therapy is, as a rule, extremely effective in its immediate results, but these results are of short duration, requiring frequent administration of the hormone in question. Except in the case of desiccated thyroid in hypothyroidism, the administration of hormones by mouth has been almost always unsatisfactory and completely ineffectual. The following hormones have proved their effectiveness clinically and can be advocated therapeutically: Insulin in diabetes mellitus; desiccated thyroid or thyroxin in myxedema and early in cretinism; pitressin in diabetes insipidus; parathormone in parathyroid tetany; and eschatin, the cortical hormone of the adrenal glands, in Addison's disease. Eschatin has already established its value in a limited clinical trial so far as immediate results are concerned. The final clinical assay so far as ultimate results are concerned is still to be made. Great promise attends the use of several other hormones but they are still in the field of clinical investigation. Hormonal therapy is assuming a new and important rôle in relation to surgery in diminishing the operative risk and mortality and by contribution to the postoperative recovery in patients afflicted with diseases of the ductless glands. The study of patients with tumors of the endocrine glands reveals, as a rule, the clinical manifestations of excessive amounts of the hormone concerned. Tumors of the endocrine glands emphasize the importance of the constitutional effects of tumors and call for a more comprehensive study of the problem involved, in relation to other types of tumors. Finally, the recent and important advances made in the fundamental fields have tremendously enhanced the opportunity for true service to the sick on the part of the clinicians. This concerns practically all the major fields of practice, especially medicine, pediatrics, gynecology, urology and surgery.—I. B.

Estrogenic substances: theelin. Report of the Council on Pharmacy and Chemistry, J. A. M. A. **100**: 1331. 1933.

A remarkably satisfactory review of a large mass of recent evidence on hormonal factors in female reproductive physiology with special reference to therapeutics. The article concludes: "The place of Theelin and related products in gynecologic therapy remains for the future to decide. Great caution is necessary in the use of these preparations and greater caution in making deductions from it. The indiscriminate use is likely to do more harm than good, not only because of the effect of the preparations themselves but also because of general therapeutic measures intended to aid the organism in restoring its own equilibrium are likely to be neglected. The Council believes that the future of endocrine therapy in the sexual sphere appears quite promising. But it is not surprising in view of the short time that has elapsed since the introduction of active preparations commercially, that little should be known about their therapeutic possibilities. Enthusiasm in this case has in large part seriously interfered with clinical judgment; the clinical use has kept far ahead of the laboratory data; controlled observations have been few indeed. It is time to call attention to the fact that most of the basic facts should first be worked out in the laboratory before they are tried in the clinic.
—R. G. H.

Basal metabolism in the menstrual and reproductive phases (Grundumsatz in den mensuellen und in den Reproduktionsphasen). v. Arvey, A. and H. Meyer, Zentralbl. f. Gynäk. **56**: 194. 1932.

The authors analyze the reported levels of ovarian hormone in the blood during the various phases of the menstrual and reproductive cycles. In earlier papers one of them (v. A.) has demonstrated an increase in the respiratory metabolism under the stimulus of ovarian preparations and, further, that this effect can be produced both in intact and in thyroidectomized animals. They report a group of 10 young women studied during mid-interval (18 observations), the pre-menstrual (7 obs.), and in menstruation (10 obs.) and record mean values of +0.4%, +6.3% and —5.8%, respectively. They conclude that a premenstrual increase and menstrual decline is established by these figures, and that the fluctuations parallel those reported of the ovarian hormone in the blood. On the basis of 28 single observations from the 2nd to the 10th month of pregnancy (18 of these reports derive from apparently two patients, the only ones presenting serial study), they conclude that Fels is correct in his report of an absence of hormone during the first three months, an irregular increase to the 7th, and a definitely sustained higher value from this point to the end of the pregnancy. All of their values are above prediction and the

average of the last month (7 obs.) is 21% above the normal. Postpartum they record a difference between nursing (10 cases, 37 obs.) and non-nursing (4 cases, 16 obs.) mothers. The first group return to normal basal levels inside of four days, the second are first normal nine days after delivery. They explain this on the ground that lactation permits a more rapid elimination of (excess) ovarian hormone than in those cases in which only the kidneys and lochia form channels for depletion. They ascribe all of the changes reported to the influence of the levels of ovarian hormone in the blood. Analysis of the rather limited and scattered data suggests an inadequacy to document completely the rather broad general conclusions based upon them.—A. W. R.

Effects of urine from pregnant women on the genital tract of guinea pigs following sympathetic enervation (Action de l'urine de femme enceinte sur le tractus génital du cobaye après énervation sympathique). Bacq, Z. M. and L. Brouha, Compt. rend. Soc. de biol. **109**: 1141. 1932.

In immature and adult guinea pigs marked enlargement of the seminal vesicle followed a course of injections of urine from pregnant women, whether or not the sympathetic supply had been destroyed by removal of the hypogastric ganglion.—J. C. D.

Action of injections of posterior hypophyseal extract on ovaries of guinea pigs (Action, sur l'ovaire de Cobaye des injections d'extraits de posthypophyse). Collin, R. and J. Watrin, Compt. rend. Soc. de biol. **112**: 61. 1933.

Female guinea pigs, weighing 275 to 365 grams, received 100 units of commercial extract in 5 or 6 doses. The ovaries, examined up to a week later, showed decrease in size owing to atresia of the follicules.—J. C. D.

Assay of male sex hormone by the fish test (Der Nachweis des männlichen Sexualhormons mit dem Fischtest). Glaser, E. and O. Haempel, Deutsche. med. Wchnschr. **58**: 1247. 1932.

Further work is reported by use of the castrated fish test. The nuptial coloration caused by the sex hormone is permanently suppressed by adrenaline, the coloration in uncastrated fish as well as that caused by yohimbin appears again after the cessation of the adrenaline reaction. The coloration effected by pituitary preparations is not suppressed by adrenaline. Since the fish unit and the lethal dose are so widely separated the detection of toxic substances and impurities is easy and affords opportunity for purification.

—E. Glaser. (Translated by J. Gagnon.)

Our fish test as a standardization method for the male sex hormone (Unser Fischtest als Standardisierungs methode des männlichen Sexualhormons). Glaser, E. and O. Haempel, Endokrinologie, **11**: 81. 1932.

For a long time chemists and doctors have been striving for an assay method for the testis hormone which would require a short test time, would not require too much special knowledge, would be easily and macroscopically recognizable, would be very sensitive, and would not be very expensive. The Glaser-Haempel fish test, based upon the nuptial coloration of the bitterling, is fitted to these conditions. It is easily recognizable, is economical, is exceedingly sensitive and requires only 6-7 hours for observation. The fish test is of more value than the cock's feather test which is now mostly used for testis hormone assay since it shows the partial as well as the total heat reaction. Also in the hands of the same experimentor the quick increase in weight of the capon together with the greater intervals between the applications change the result of the assay in many cases. The testis hormone can be separated from yohimbin both chemically and hormonally. The "erythrophore" reaction caused by pituitary extracts (Pituisan, Praepitan, Intermedin) is also easily distinguished. This reaction within a certain dose is not suppressed by adrenaline, while the reaction caused by the testis hormone and by yohimbin is abolished by adrenaline in either castrated or normal male bitterlings. The nuptial coloration effected by yohimbin appears again in castrated and normal fish after the cessation of the adrenaline action.

—E. Glaser. (Translated by J. Gagnon.)

The effect on lactating mice of injecting an extract of the urine of pregnancy. Enzmann, E. V. and G. Pincus, Am. J. Physiol. **103:** 30. 1933.

Pregnancy urine extracts (antuitrin) potent as agents in ovarian luteinization, exert definite deleterious effects on lactating efficiency when continuously injected into nursing mice. Beginning on the day of birth of the young daily injections of from 0.25 rat units to 20 rat units were made in 7 groups of animals, each group consisting of five females (of a homogeneous inbred line) nursing four young each; and daily injections of normal saline solution were made in a similar control group. When comparisons were made with the standard growth curve of this strain it was noted that with increasing dosage the mean growth rate was much reduced. Furthermore, the greater the dosage the greater the mortality of the young such that the number dying was roughly proportional to the logarithm of the dosage injected. Extracts which, by long standing, had lost gonad-stimulating effects, had no effect either on the growth or mortality of the young.—Authors' Abst.

Note on the effect of the uterus on the corpora lutea during pregnancy in the guinea pig (A propos des interactions entre l'utérus et le corps jaune au cours de la grossesse chez le Cobaye). Desclin, L., Compt. rend. Soc. de biol. **109:** 972. 1932.

Hysterectomy was performed on animals of about 600 grams body weight at various stages in pregnancy. This operation was followed by a persistence of the corpora lutea of pregnancy with a resulting period of pseudo-gestation lasting up to three months.—J. C. D.

Precocious development of sexual characters in the fowl by daily injections of hebin. Domm, L. V. and H. B. Van Dyke, Proc. Soc. Exper. Biol. & Med. **30:** 349. 1932.

These reports deal with the effect of the daily administration of hebin, a purified gonad-stimulating hormone prepared from sheep pituitary glands. In the first report the preparation was given to light brown Leghorn cocks and their juvenile sex character changes were studied largely by the head furnishings, which were measured at regular intervals. The treated cocks remained in good physical condition despite the daily injections of from 4 to 32 rat units over a period of 14 to 36 days. The first effect observed occurred, in some instances, as early as 48 hours after injections began, as a pronounced stimulation of head furnishings. These began rapidly to increase in size and the young cocks soon were attempting to crow. The autopsies revealed hypertrophy of the testes in the treated individuals, which were larger and heavier than in the untreated birds. The thyroid glands were likewise larger and heavier. Other organs did not show any significant change, but distinct histologic modifications were found in the testes of the experimental birds. These observations confirmed Domm's previous work. It is assumed that the injected gonad-stimulating hormone acted directly on the thyroids and gonads and that the precocious development of the testes accounts for the development of other sexual characters. In a second paper which has to do with the female bird there is noted likewise the phenomenal growth of head furnishings together with considerable hypertrophy of the ovaries as contrasted with the controls. Here again the thyroid showed perceptible hypertrophy. It is assumed that the injected gonad-stimulating hormone in the stimulation of the gonads brought about a precocious endocrine, rather than gametogenetic, functioning responsible for the development of the other sexual characteristics.
—M. O. L.

True menstrual bleeding in castrated women after treatment with follicle and corpus luteum hormones (Echte menstruelle Blutung bei kastrierten Frauen nach zufuhr von Follikel-und corpus luteum-hormon). Kaufmann, C., Klin. Wchnschr. **12:** 217. 1933.

The author reports a second clinical experiment with the use of huge doses of follicular hormone (progynon) and luteal hormone in castrated women. In a previous paper he reported actual uterine bleeding from a pregravid endometrium in a castrated woman after treatment with the two hormones of the ovary, namely, estrin and progestin. This phenomen was brought about by the use of 320,000 mouse units of progynon-benzoate and 90 rabbit units of luteohormone. Twenty-four hours after the last injection of luteal hormone, bleeding occurred which lasted for three days. Microscopic examination of parti-

cles of tissue cast off in the discharge disclosed a proliferative endometrium. In the second experiment, the subject was a woman of 40 years who had undergone bilateral oöphorectomy two years previously because of cystic ovaries. Preliminary curettage disclosed a high grade atrophy of the endometrium. For the next 16 days she received 300,000 mouse units of progynon-benzoate in 30 injections. This was followed by six daily injections of 10 rabbit units of luteo-hormone (60 units). Two days after the last injection she began to bleed. On the second day she passed tissue which on examination proved to be pregravid endometrium.—L. Goldstein.

Effects of castration and destruction of the corpora lutea in the latter half of pregnancy on gestation in rabbits (Effets de la castration et de la destruction des corps jaunes au cours de la deuxième partie de la grossesse chez la Lapine). Klein, M., Compt., rend. Soc. de biol. **109:** 932. 1932.

In six rabbits the ovaries were removed between the twentieth and twenty-fifth day of pregnancy. In six others, all corpora lutea were destroyed with a cautery. All animals aborted. Operated controls did not abort.—J. C. D.

Crystalline male hormone (L'ormone maschile cristallizzato). Maino, M. and B. Frattini, Boll. d. Soc. ital. di biol. sper. **7:** 55. 1932. Abst., Physiol. Absts. **18:** 140.

The authors' crystalline testis extract was sublimed 3 times at 80° to 90° in vacuo, in order to separate the male hormone from any folliculin, which distills at 150° C. After this treatment the crystals obtained showed undiminished capacity for promoting the growth of the comb of castrated cocks and also induced oestrus in castrated female rats.

Ovarian tumors of thyroid tissue. Masson, J. C. and Selma C. Mueller, Surg., Gynec. & Obst. **56:** 931. 1933.

Five cases of ovarian tumor containing large amounts of thyroid tissue are presented. In one case the ovarian tumor contained nodules of hyperplastic thyroid tissue. Tumors of thyroid tissue in the ovary are probably of the nature of teratomata. Since these tumors are of thyroid tissue, they are potential sources of thyroxine and in some cases seem to produce hyperthyroidism. Three of the tumors were analyzed for iodine and an appreciable amount was found. Hyperplasia of the thyroid epithelium, in varying degrees is commonly observed in these tumors. Malignant changes were not observed in the tumors reported in this series. Ascites is not infrequently an accompaniment of these tumors.—Authors' Summary.

The production of mucification of the vaginal epithelium of rodents by the oestrous hormone. Meyer, R. K. and W. M. Allen, Science, **75:** 111. 1932.

Mucified cells in the vaginal epithelium of castrated rats can be produced by corpus luteum extracts containing progestin and probably small amounts of oestrin. The same reaction was elicited in castrated adult mice and guinea pigs and in non-castrated immature guinea pigs by the injection of the crystalline oestrous hormone (theelin). Mucification indistinguishable from that seen in mice in late pregnancy was produced in adult mice which were castrated in oestrus and given from 0.04-0.06 r. u. theelin per day for 8 days. Mucification was also produced in castrated mice by the injection of oestrin obtained from male urine. In the adult guinea pig castrated in oestrus 0.5 r. u. theelin per day for 25 days produced mucification equal to that seen early in the second month of pregnancy. Mucification of the vaginal epithelium cannot be used as a test for the specific substance contained in the corpus luteum and responsible for progestational proliferation of the rabbit's uterus (progestin).

—R. K. Meyers.

Action of theelin on the domestic fowl. Mitchell, J. B., Jr., Proc. Soc. Exper. Biol. & Med. **30:** 500. 1933.

The crystallin product, theelin, is effective in restoring to female fowl type those secondary sex characters which have been altered by ovariectomy—namely, feathers and oviduct. With 3 weeks' injection, theelin does not interfere with the stimulus to comb-growth afforded by the compensatory right gonad in this species. Olive oil solution is more effective in producing these results in the fowl than is saline solution.—M. O. L.

The excretion of ovary stimulating hormone in the urine during pregnancy. Murphy, D. P., Surg. Gynec. & Obst. **56**: 914. 1933.

The amount of ovary-stimulating hormone (expressed in rabbit units) in 30 24-hour specimens of urine of 24 pregnant women is recorded. Some patients were normal; others exhibited mild complications of pregnancy; the majority were in the last third of gestation when their urine was collected. The amount of hormone excreted in 24 hours varied from less than 100 to more than 12,000 rabbit units; the majority of patients voided less than 2,000 rabbit units. The excretion of hormone by the same individual from day to day was relatively constant and was independent of the output of urine. From these observations it is concluded that: (1) Variation in the output of urine has no significant influence upon the amount of ovary stimulating hormone which is excreted. (2) Estimation of the rate of excretion of ovary stimulating hormone should be based upon measurement of the hormone in the urine that is passed in a 24-hour period, and not upon the amount in a smaller sample of urine.—Author's Summary.

The hormone of the anterior lobe of the pituitary (prolan) and the male gonads (Hypophysenvorderlappenhormon [Prolan] und die Männliche Gonade). Neumann, H. G., Zentralbl. f. Gynäk. **55**: 407. 1931.

The author has studied the effect of injecting a dose of 200-400 rat units of prolan on a series of 40 male mice of 6-8 gm. body weight. He reports no essential difference in body or testicular weight between the injected and control animals. Histologically he found increased spermatogenesis, in some cases to full development, in the injected animals. These also showed regularly enlargement of seminal vesicles and other secondary organs. He found, however, that body weight is not a certain indication of the extent of sexual development, since controls of equal body weight often showed varying degrees of testicular development. Age, on the other hand, proved to be a good criterion. The author suggests the following procedure for prolan assay on males: Injection of prolan into immature male mice, always less than 26 days old, over a period of 48 hours, in 6 doses equivalent to those in the Aschheim-Zondek test. Upon killing after 100 hours the following criteria are to be looked for: (1) Increased mitoses of spermatogonia and spermatocytes; lumen formation of seminiferous tubules; (2) evident enlargement of seminal vesicles as well as other secondary organs.—O. S. Baum.

The continued injection of oestrin into young rats. Pincus, G. and N. Werthessen, Am. J. Physiol. **103**: 631. 1933.

Continued injection of oestrin (theelin) into young rats resulted in inhibition of ovarian growth and in a certain amount of thyroid hypertrophy, but no definite effect on the weight of either the anterior or posterior lobe of the pituitary. The most consistent effect was the inhibition of ovarian growth. The extent of inhibition was not proportionate to the range of dosages employed (1 to 10 rat units per day), but was proportionate to the number of days of injection, such that over the age-range employed the extent of inhibition increased logarithmically with time. Injections were made from 5 to 40 days in the various groups of animals employed.—G. Pincus.

Existence of menstrual cycle in the labia minora (Existence d'un cycle mensuel dans les petites lèvres humaines). Rainer, M. T., Compt. rend. Soc. de biol. **112**: 75. 1933.

Two specimens were removed, one seven and one 16 days after menstruation. The latter showed enlargement of the cells and increase in mitoses as compared with the former.—J. C. D.

Swelling of the external genitalia in castrated female baboons after oral and hypodermic treatment with female follicular sex hormone. Schoeller, W., M. Dohrn and W. Hohlweg, J. Lab. & Clin. Med. **18**: 926. 1933.

Experiments on 5 animals are reported which showed that with the peroral administration of 6,000 to 8,000 rat units of progynon spread over a period of eight days, the genital swellings characteristic of heat can be reproduced in the castrated female baboon. With subcutaneous injection of crystalline follicular hormone dissolved in oil 2,000 rat units spread over a period of eight

days produced the same effect, while the same dose given in a single injection is inactive. If, however, progynon benzoate is used, a single injection of 2,000 rat units is sufficient to produce a definite reaction. Our investigations once again demonstrate that with a suitably chosen product and tablets of a particular composition, the peroral dose is only four to five times greater than the parenteral one.—R. G. H.

Connections between intermittent articular dropsy and ovarian function (Zur Frage der Zusammenhänge zwischen Hydrops articlorum intermittens und Ovarialfunktion). Vogl, A., Wien. klin. Wchnschr. **45:** 1344. 1932. Abst., J. A. M. A. **100:** 151.

According to Vogl, most authorities are of the opinion that the comparatively rare intermittent articular dropsy belongs to the angioneurotic disturbances, more particularly to the group of neurotic edemas, while others think that it is due to a dysfunction or hypofunction of the ovaries. As proof that disorders of the ovarian function cannot be the only pathogenic factor of intermittent articular dropsy the author cites the fact that the disorder occurs also in men and that in women the intervals between recurrences are frequently independent of the menstrual cycle. Moreover, not all cases respond to treatment with ovarian extracts and the disorder may entirely disappear for months and even years. The latter occurrence can sometimes be traced to intense psychic alterations. The author thinks that intermittent articular dropsy is due partly to constitutional inferiority of the articular apparatus, for there is a high incidence of articular disorders in the families of these patients, and partly to a constitutional angioneurotic factor. That in some patients the attacks concur with the menstrual period he considers due to the fact that during this period the irritability and permeability of the vascular apparatus are increased. He warns against a one-sided evaluation of intermittent articular dropsy as an endocrine, particularly an ovarian, disorder and, although ovarian extracts may occasionally prove helpful, he thinks that it is wrong to consider a case as incurable if ovarian extracts do not improve the condition. On the contrary, various cases have been found to respond to different measures, to hydrotherapeutics, to salt-free diet, to a cinchophen preparation, to injections of arsenic, to the various forms of ovarian preparations, to change of climate and to hypnosis. The author thinks that the psychologic factor is probably quite often the most significant one, that most of these therapeutic measures are largely nothing but a masked psychotherapy, and that spontaneous remissions are possible.

Development of the testicles and connected urogenital structures in cattle (Die Entwicklung des Testikels und der Urogenitalverbindung beim Rind). van Vloten, J. G. C., Ztschr. f. Anat. u. Entwcklngsgesch. **98:** 578. 1932.

Largely morphological. It was found that the interstitial cells are first recognizable in the 28 mm. stage of the embryo. After 30 mm. there is a noticeable increase in these elements of the testis. At about birth there is a relative decrease in the interstitial cells. Many of them lose much of the cytoplasm. Still later, they show a relative increase again. During fetal life there is very little lipoid in the interstitial cells. Three different interpretations of the origin of the interstitial cells are briefly reviewed.—A. T. R.

A new method for the separation of the male sex hormone from the female hormone (Eine neue Methode zur Trennung des männlichen Sexual hormons vom weiblichen Sexualhormon (Follikelhormon). Wadehn, F., Endokrinologie, **12:** 241. 1933.

Ten litres of urine are mixed with 200 cc. of concentrated hydrochloric acid and allowed to stand for a few days. This acidification splits up the peptides which would form an emulsion when shaken with benzol. The urine is then shaken several times with benzol and the combined benzol solution washed with neutral water and evaporated. The residue is taken up with 300 cc. for a 10% caustic soda solution and heated until all the benzol is driven off. This leaves a dark brown solution, which is vigorously shaken repeatedly with half the amount of benzol. The brown benzol solution is washed with water, evaporated to 150 cc., vigorously shaken for a few minutes with 10 cc. of 75% sulphuric acid. This procedure is repeated three times. The operation separates the two hormones, the follicular hormone remaining in the benzol solution while the male hormone goes into the sulphuric acid solution. The sul-

phuric acid solution is then diluted until the acid content is 20%. From a sulphuric acid solution of this concentration the male sex hormone is easily extracted in the usual manner by benzol or ether.—J. Gagnon.

Studies on the menstrual cycle of Macaccus rhesus monkeys and observations on the mechanism of menstrual flow (Studies über den Sexualzuklus bei Makakus-rhesus-Affen, nebst einigen Bemerkungen über den menstruellen Blutungsmechanismus). Westman, A., Acta obstet. et gyn. Scandinav. **12:** 282. 1932.

Westman studied the menstrual cycle of seven "full-grown" rhesus females for from 6 to 18 months, at the end of which time he killed them in different periods of the menstrual cycle and submitted the ovaries and genital tracts to careful histological analysis. The well-known changes in the ovaries, uteri, and vaginae are described—five animals in ovulatory, two in non-ovulatory cycles. The results are corroborative of previous work on the human and the monkey female. The author attempts to homologize the menstrual cycle of primates with the oestrous cycle of lower mammals. In the former there is no interruption of the pro-oestrous proliferation in connection with the rupture of the follicle, but goes on through the luteal phase. This conclusion is based chiefly on vaginal changes. The author, therefore, accepts the "telescoping" theory of Marshall as modified by Zuckerman, namely, that the prooestrous bleeding of lower forms is postponed by means of continued oestrin secretion of the corpus luteum or follicle to the time of their degeneration. A clear distinction is made between ovulatory and non-ovulatory menses ("pseudomenstruation"). Of greatest significance is the author's correlation between the uterine motility and its effect on the blood flow through this organ. Increased contraction cuts off the blood supply, which results in necrosis and desquamation with bleeding, i.e., menstruation. This is, in the reviewer's opinion, a much neglected factor in the study of the physiology of menstruation.—C. Hartman.

Hormonal analysis of urine and of secretion of mammary gland (Hormonanalysen im Urin und im Brustdrüsensekret. Beitrag zur Biologie und Pathologie der Brustdrüse in und ausserhalb der Schwangerschaft). Winter, E. W., Arch. f. Gynäk. **151:** 201. 1932. Abst., J. A. M. A. **100:** 150.

In the urine of the new-born child the ovarian hormone is present up to the third day after birth and the hormone of the anterior lobe of the hypophysis up to the ninth day. The mammary secretion of the newly born contains no hormones. In the colostrum of pregnant women the hormone of the anterior lobe of the hypophysis is present from the seventh month on and remains present in the mammary secretion up to the sixth day of the puerperium. The ovarian hormone is not present in the colostrum. In patients with hydatid mole, the hormone of the anterior hypophysis is present in the colostrum much earlier than during normal pregnancy. During the first stage of the menopause the urine contains the ovarian hormone, but during the last stage, as well as in genital carcinoma, pruritus vulvae and leukoplakia vulvae the urine frequently contains the follicle maturation hormone. Hormonal analysis of the urine of sexually mature women with menstrual anomalies does not explain the disturbance or give information about a suitable therapy. During dysmenorrhea the urine frequently contains the follicle maturation hormone, but during sterility none of the hormones are present in the urine. In cases of amenorrhea it is frequently possible to produce with the urine the anterior hypophyseal hormone reactions (I and II). The author thinks that the mammary secretion during pregnancy, in the newly born, during false pregnancy, amenorrhea and similar disturbances is due to a disturbance in the correlations between the ovarian and the hypophyseal hormone with involvement of the sympathetic nervous system; a predominance of the anterior lobe of the hypophysis is probably the principal cause.

The antagonistic action of the thyroid-stimulating component of the anterior lobe of the hypophysis and folliculin from the ovary on the function of the hypophysis (Action antagoniste de la thyréo-stimuline préhypophysaire et de la folliculine ovarienne sur le fonctionnement thyroïdien). Aron, M. and J. Benoit, Compt. rend. Soc. de biol. **109:** 923. 1932.

Over 40 young guinea pigs of about 200 grams weight received injections of anterior lobe extract and of folliculin. If they had received anterior lobe

alone, the thyroid would have shown signs of great activity 27 to 36 hours afterward. When the two extracts were injected, these signs did not appear.
—J. C. D.

Characteristics of the Golgi apparatus in the different types of cells of the anterior hypophysis. Atwell, W. J., Anat. Rec. **55**: 11. 1932.

The cells of the anterior lobe of the cat's hypophysis have been studied after preparation by a variety of staining methods. These include Da Fano's modification of the Cajal silver method for the Golgi apparatus followed by such stains as Mallory's connective-tissue stain or Heidenhain's Azan; Mann-Kopsch osmo-sublimate, and Champy-Kull-Nassonow. Some methods demonstrate Golgi apparatus, cytoplasmic granules, and mitochondria in the same preparation. The Golgi apparatus is found to possess differential characteristics in the several varieties of cells of the anterior lobe. In the eosinophiles the net is small (averaging 3.65 μ x 2.58 μ) dense, somewhat flattened and closely applied to the nucleus. In the basophiles the net is larger (averaging 5.48 μ x 3.87 μ) and looser. The chromophobes usually contain the largest nets (averaging 6.86 μ x 5.62 μ) which are more spherical, more loosely arranged and more distant from the nucleus than in the chromophile varieties. Chromophobes containing the type of Golgi net characteristic of the eosinophiles have been observed but are relatively few in number in the cat's hypophysis. The centrosome, commonly as a diplosome, is found in the interior of the Golgi apparatus. The possible significance of the above observations in relation to the lineage of the different varieties of cells is discussed.—Author's Abst.

Effects of administration of cortin to the hypophysectomized rat. Atwell, W. J., Proc. Soc. Exper. Biol. & Med. **29**: 1259. 1932.

Hypophysectomized albino rats were treated with cortin. There was no repair of the atrophy characteristically following hypophysectomy, of the gonads, thyroids or adrenal cortex. The oestrous cycles were not restored, nor was the growth rate increased. In other respects, the cortin-treated rats were strikingly different from the untreated. Instead of being cold, apathetic, and inactive, they were distinctly active with body temperatures near normal.
—M. O. L.

Presence of a melanophore dilating substance in the tuber cinereum of guinea pigs (Présence d'un principe mélanophoro-dilatateur dans le tuber cinereum du Cobaye). Collin, R. and P. L. Drouet, Compt. rend. Soc. de biol. **112**: 63. 1933.

Tuber cinereums with more or less of their surrounding nervous tissue were transplanted into 13 frogs. Five of these showed dilatation of the melanophores.—J. C. D.

"Dyspituitarism": Twenty years later. With special consideration of the pituitary adenomas. Cushing, H., Arch. Int. Med. **51**: 487. 1933.

This article is impossible to treat satisfactorily in an abstract. It is probably the best discussion of pituitary functions in relation to clinical conditions that has ever been written. It should be read in its entirety. The selected bibliography of 139 titles is noteworthy. The author concludes: "During the past two decades much has been learned about pituitary dysfunction from many angles: from comparative and experimental zoology most of all; from clinical pathology a great deal; something from histologic cytology; and as yet, all too little from biochemistry to which we pin our chief hope. Whereas the pituitary body was once looked on as a functioning whole, this idea was disrupted when Howell showed in 1898 that its blood pressure-raising effect was confined to extracts of the posterior lobe. Since then an ever-mounting number of properties suggesting separate chemical messengers have come to be ascribed to one or another subdivision of the gland—those of the posterior lobe giving acute pharmacodynamic responses, those of the anterior lobe producing their effects more slowly. After Howell's discovery, fifteen years passed before it was found that posterior lobe extracts could control diabetes insipidus, and ten years more before the relation of this disorder to certain clusters of nerve cells in the hypothalamus was appreciated. And now after a lapse of thirty-five years, the fact that posterior lobe overactivity may be responsible for a number of hitherto obscure clinical disorders has only begun to be realized.

Attention meanwhile has been chiefly focused on the properties of anterior lobe extracts whose remarkable effects have served further to emphasize the dominance of the gland over other members of the endocrine series. Much, indeed, that has already been done in studying these subsidiary glands as isolated and independent structures needs redoing and reinterpreting. And at the same time the conception that anterior lobe, posterior lobe and interbrain work in harmony and cannot well be studied separately has been clearly demonstrated. The pituitary adenomas have been made the subject of this lecture with the intent of drawing renewed attention to these processes as secretory 'stills' which, in spite of their pathologic structure, nevertheless in all probability are elaborating an excess of the normal hormones. Not until we have learned how to incite in experimental animals an actively and continuously secreting lesion of this sort can we expect precisely to reproduce, and thereby fully to interpret the effects of Nature's prolonged experiment on man. In order to gauge what substance, if any, is secreted by the different adenomas, the patient's blood and urine as well as tissue from the tumor itself when available will some day have to be tested for the presence of each of the accepted as well as of the several predicated hormones of the normal gland. But only when these tests come to be more simplified than they now are will it be possible definitely to say: whether a chromophobe adenoma, like that of the dwarfed child, actually has any secretory product; whether the overgrowth in lads like those described is due to an excess of the growth principle; whether or not the blood of the acromegalic woman was flooded with a separable lactogenic hormone; and what may have been the nature of the substance elaborated by the tumor in the case of the unfortunate woman so long victimized by pituitary basophilism."

—R. G. H.

The influence of the thyreotropic substance of the anterior lobe of the hypophysis and the sex-stimulating principle upon respiratory metabolism (Untersuchungen über die Beeinflussung des respiratorischen Stoffwechsels durch Hypophysenvorderlappensexualhormon und thyreotropen Wirkstoff). Diefenbach, O. L., Endokrinologie, **12:** 250. 1933.

Using adult and immature rats and guinea pigs the normal metabolism was determined in a closed circuit apparatus. After subsequent treatment with thyreotropic substance and with the pituitary sex hormone the gaseous metabolism was determined with the following results. Anterior lobe sex hormone from urine of pregnancy did not affect the metabolism of adult male guinea pigs or of immature female rats. Injection of varied amounts of thyreotropic substance increased the metabolism of adult rats and guinea pigs with the increase dependent upon the quantity of hormone used. This metabolic rise was demonstrated in rats 1½ hours after injection, in guinea pigs after 24 hours. Twenty-four hours after the injection the metabolic rate had fallen greatly in the rats, the guinea pigs showed a slow decrease 48 hours after the injection. Thyreotropic substance causes no rise in gaseous metabolism in thyroidectomized animals but a fall below the normal takes place.—J. Gagnon.

The anterior pituitary sex hormone of normal and semi-castrated rats. Emery, F. E., P. W. Bash and W. R. Lewis, Proc. Soc. Exper. Biol. & Med. **29:** 42. 1931.

The amount of anterior pituitary sex hormone in the pituitaries of normal male and female rats was not noticeably changed after semicastration. This hormone was not found in the blood serum of normal or semicastrated nullipara females, or in normal or semicastrated males. The need for a greater amount of the hormone in the blood of semicastrated animals is pointed out.

—Authors' Summary.

Metabolic changes following the intravenous injection of posterior pituitary extracts and their correlation with the well-known pharmacodynamic actions of the drugs. Geiling, E. M. K. and A. M. DeLawder, Bull. Johns Hopkins Hosp. **51:** 1. 1932.

The action of pituitary extracts—pituitrin, pitressin and pitocin—on metabolism was investigated by studying the changes in certain blood constituents produced by single, intravenous injections of the extracts into normal, unanesthetized dogs. It was found that blood drawn from the saphenous or deep femoral veins 3-8 minutes after the injection of pituitrin or pitressin is characterized by an arterial-like color and oxygen content, a lowered carbon dioxide

tension, a rapidly rising lactic acid concentration, increased glucose and inorganic phosphate. This period of anaerobic metabolism in the tissues drained by these vessels is followed by a second stage in which the conditions are reversed: an abnormally dark venous blood of subnormal oxygen content (indicating increased oxygen consumption by the tissues), an increase in carbon dioxide, and a continued rise of lactic acid, with subsequent slow restoration to the preinjection level. The blood is essentially normal in one and one-half to two hours after injection. Inactivation of pitressin by treatment with alkali produces a loss of these physiological properties. In contrast to the arterial-like blood draining the limbs in the anaerobic stage, the blood of the external jugular vein is more venous in color and has a decreased oxygen content. Commercial pitocin gives a transient pitressin effect, while purified pitocin produced in some cases an increase in metabolism. The causative mechanism for the pituitrin or pitressin effect is viewed as operating either through the vascular system or a direct action of these drugs on the cells, or both. The authors propose the following hypothesis: If we postulate that the action of the extracts represents that of the posterior pituitary hormone as it exists in the body, and that the injection of such extracts, although it be a crude imitation under exaggerated conditions, simulates the normal action of the hormone, then the posterior lobe of the hypophysis functions in the body as one of the regulators of metabolism.—Authors' Abst.

Changes in total gaseous metabolism of unanesthetized dogs after intravenous injection of posterior pituitary extracts. Geiling, E. M. K. and A. M. DeLawder, Bull. Johns Hopkins Hosp. **51**: 335. 1932.

The intravenous injection of pituitrin or pitressin in doses ranging from 0.2-0.6 cc. produced an immediate and precipitous decrease in the total oxygen consumption of the body as measured on trained unanesthetized dogs by the Douglas bag technique. This depression of metabolism was followed about 10-15 minutes after injection by a prompt rise to a value considerably above the pre-injection level, and then a gradual return to the base line. The changes parallel the alteration in blood gases previously described. Pitocin, although not consistent in its effect, produced an increase in oxygen consumption in the majority of tests.—Authors' Abst.

Synergistic effect of anterior pituitary and male hormone. Graber, H. T. and R. A. Cowles, Proc. Soc. Exper. Biol. & Med. **30**: 384. 1932.

The synergistic effect of the anterior pituitary sex hormone and male hormone was demonstrated by treating both mature and immature rats with anterior pituitary hormone alone, male hormone alone, and both hormones simultaneously. The experiments were made at two ages, with rats at 6-7 weeks and at 4 months, two rats being used in each series, at each age. Assayed extracts from anterior pituitary and fresh testis material were used. The seminal vesicles were not enlarged under the influence of the small doses of testis extract used but these doses in combination with pituitary extract caused considerably greater hypertrophy than did the latter alone. The results in the testes were irregular but hypertrophy occurred in some cases.—R. G. H.

Effect of acid extract of anterior pituitary on heart rate, and nervous irritability of guinea pigs. Hageman, P. O. and H. A. McCordock, Proc. Soc. Exper. Biol. & Med. **30**: 297. 1932.

The heart rates of guinea pigs, determined by the electrocardiograph, were increased by the injection of acid extracts of beef anterior pituitary. The increase attained its maximum of about 30% in 4-12 days. Similar injections into thyroidectomized guinea pigs had only a slight transitory effect on the heart rate.—M. O. L.

On the difference between prolan A derived from pregnant women and from castrates (Sur la différence entre le Prolan A, provenant de Femmes enceintes et de castrats). Hamburger, C., Compt. rend. Soc. de biol. **112**: 99. 1933.

Prolan A from pregnant women produces a marked enlargement of a few ovarian follicles when injected into immature mice, while prolan from castrates causes a moderate enlargement of a large number of follicles. The

uterus following prolan from pregnant women is dilated with fluid and has thin walls, while, after prolan from castrates, the walls are thickened and wrinkled. One rat unit of prolan A from pregnant women equals five mouse units, while one rat unit of prolan A from castrates equals one-half a mouse unit. Probably the type of prolan A found in pregnancy comes from the placenta and that in castrates from the hypophysis.—J. C. D.

The action of posterior pituitary extract in controlling the growth of malignant tumors. Houston, S. W. and J. Miller, Tr. Roy. Soc. Canad. **26**: 71. 1932.

Nine cases of malignancy affecting different parts of the body were treated with heroic doses of pituitrin for varying periods. This treatment was combined with the administration of theelin and with a diet low in carbohydrates. The results obtained could not be regarded as uniform. In several instances, one an epithelioma of the face, one an epithelioma of the nose, one a carcinoma involving both breasts, one a carcinoma of the cervix uteri, and one a rodent-ulcer, clinical evidence of reduction in size of the growth was obtained, and in the case of the breast there was entire disappearance of active cancerous tissue in the breast and glands. In another instance (carcinoma of the prostate) there was marked relief of pain in the bones, suggesting diminution in size of secondaries. In no instance was there evidence of any ill effects which could be put down to the administration of the extract. The blood pressure and the urine were both observed over long periods. A slight temporary rise in blood pressure was the rule, but no marked reduction in the amount of urine was observed. In two instances the administration of the drug was accompanied by great pain in the growth itself, a feature noted in several of Susman's cases. It was possible to observe the effects upon the tumor cells in several cases by repeated biopsies as well as by microscopic examination after death of the patient. Neither as regards the amount of necrosis nor in the activity of cancer cells, as evidence by the number of mitotic figures, could it be said that the treatment affected the malignant process except in the case of the carcinoma of the breast, where disappearance of the breast growth occurred also necrosis of the secondaries in the axillary glands.—Authors' Summary.

The use of amidopyrine in a case of diabetes insipidus. Kahn, B. S., J. A. M. A. **100**: 1593. 1933.

The history is briefly reported of a man who was physically normal except that he suffered from well-marked diabetes insipidus. The average urine output was 6200 cc. The condition was fairly satisfactorily controlled by hypodermic injections of post-pituitary extract except that the vasomotor reaction was rather marked, leading to intense blanching of the face. Numerous attempts to alleviate the condition by the intra-nasal use of sprays and tampons saturated with a potent preparation of double strength pituitary solution were without avail as was also the use of desiccated whole pituitary gland as a snuff. Amidopyrine was substituted for the pituitary treatment, the dosage being 15 grains immediately before retiring. The urine output was controlled and specific gravity increased to 1.009. The regimen that ultimately proved most satisfactory was 15 grains of the drug for three successive nights and on the fourth night an ampule of pitressin, with 15 grains of amidopyrine at noon. On this schedule the urine output was kept down to about 4000 cc. The only side-effect of the drug was a transient light-headedness for a short time after each dose.—R. G. H.

Familial adiposogenital dystrophy and cranial defects (Distrofia adiposogenitale famigliare ed alterazioni craniche). Lucherini, T., Policlinico **40**: 53. 1933. Abst., J. A. M. A. **100**: 702.

Lucherini made a study of a man, aged 21, his brother and his sister, who all presented familial adiposogenital dystrophy of the same type. Roentgen examination revealed in all some evidence of acromegaly and thickening of the bony shell of the frontal region, with areas of greater transparency, pronounced depressions for the diploic canals and a marked depression of the occipital fossa. The markings on the bones caused by the cerebral convolutions were especially apparent on the frontal bone. There were small erosions of the inner table of the cranium. In the lateral aspects there were exaggerations of the lacunar diploic system. The sigmoid or the transverse sinus was prominent behind the solid part of the petrous portion of the temporal bone. The

author maintains that the dystrophy did not follow a lesion of the pituitary body but was the result of some obscure primary or secondary lesion of hypothalamic nerve centers. This coincides with the modern concept of a diencephalohypophyseal genesis of the disease. All three patients had a positive Wassermann reaction, the infection presumably coming from the paternal side. This the author deems important in the causation of the neurohypophyseal and cranial syndromes. The osseous alterations of the cranium together with the general clinical symptomatology made possible a diagnosis of endocranial hypertension and suggested the idea of an osteodystrophy of probable endocrinopathic origin. The author finds these cases interesting from the standpoint of roentgenology and also because of the light they throw on the still unclarified neurohypophyseal clinical syndrome.

Carbohydrate metabolism in diseases of anterior lobe of hypophysis. Lucke, H., Ztschr. f. klin. Med. **122**: 23. 1932.

The disturbances of carbohydrate metabolism accompanying acromegaly are characterized by a high fasting blood sugar (with or without glycosuria), elevated renal threshold for sugar, reduced hyperglycemic reaction to sugar and epinephrin, strong and prolonged hypoglycemic phase following alimentary hyperglycemia, and a remarkable insusceptibility to insulin. Opposite findings are encountered in cases of hypophyseal dwarfism. Lucke reports seven cases of this condition. He finds that the fasting blood sugar varies between 64 and 90 mg. per 100 cc. blood; alimentary hyperglycemia is more pronounced than it is in acromegaly; but the renal threshold for sugar is high, so that glycosuria is slight or absent. The hypoglycemic after-phase is pronounced and may reach a dangerously low level. Finally, hypophyseal dwarfs are very sensitive to insulin. Even small doses, that elicit a barely perceptible result in normals, may cause marked lowering of the blood sugar level. Similar results are found in cases of hypophyseal cachexia (Simmonds' disease) which, like dwarfism, depends on hypofunction of the anterior lobe of the pituitary body. The author concludes that the anterior lobe of the hypophysis contains an active factor that takes part in carbohydrate metabolism. Hyper and hypofunction of this lobe lead to characteristic disturbances in the regulation of that metabolism.
—H. Ulrich.

Reciprocal relationship between ovaries and anterior hypophysis as factor in control of lactation. Nelson, W. O., Proc. Soc. Exper. Biol. & Med. **30**: 953. 1933.

The injection, into pregnant guinea pigs, of a potent anterior lobe gonad-stimulating extract terminated pregnancy and induced lactation (8 cases). Extirpation of the ovaries did not invariably lead to abortion (7 out of 21 cases went to term). Lactation occurred only after foetal expulsion whether abortive or at term. Surgical removal of the entire pregnant uterus did not cause lactation unless the anterior lobe extract was administered (11 cases). Surgical removal of the uterus and the ovaries did induce lactation (5 cases). Surgical removal of the ovaries and the fertile uterine horn only, in cases of unilateral pregnancy, resulted in lactation (4 cases). Lactation did not occur when the ovaries and embryos were removed, leaving the placentae intact, during the period of placental retention, but did occur following expulsion of the placentae (4 cases). Autopsies of animals failing to lactate following natural, although abnormal, deliveries has revealed the retention of placental tissue. Lactation may be induced in such animals by administration of anterior lobe extracts. Lactation was inhibited in normal parturient females by theelin administration (5 cases). However, if an anterior lobe extract was administered simultaneously with the theelin, lactation occurred (3 cases).—M. O. L.

The incidence of tubular glands and concretions in the adult human hypophysis cerebri. Rasmussen, A. T., Anat. Rec. **55**: 139. 1932.

Systematic exploration of series of sections from 111 male and 124 female carefully selected adult normal hypophyses, from 19 to 84 years of age, indicate that tubular, gland-like structures belonging to pars intermedia, but sometimes extending well into the posterior lobe, are present in about 49% males and 78% females. The percentage is less in case of females over 50 years of age, but the difference is not statistically significant. There is no significant difference in the incidence of tubular glands in 24 pregnant as compared with 64 non-pregnant females of similar age. Concretions resembling "brain sand"

were present in the pial investment on the upper aspect of the hypophysis of 37% of the males and 71% of the females. There was no difference in the percentage in those over 50 years as compared with those under 50 years of age, nor in pregnant individuals. No evidence was found of the purported patent communication between the residual lumen and the venous blood sinuses.
—Author's Abst.

Changes in the teeth following hypophysectomy. Changes in the incisor of the white rat. Schour, I. and H. B. Van Dyke, Am. J. Anat. **50:** 397. 1932.

A study was made of the gross and microscopic anatomy and the rate of eruption of the incisors of 23 successfully hypophysectomized rats. Their age when operated upon ranged from 36 to 64 days and the postoperative life ranged from 63 to 459 days. This gave a sufficiently complete series of stages so that the regressive changes could be followed. A similar study was also made of 16 litter-mate controls, most of which were unsuccessfully hypophysectomized. Significant changes were observed only in the successfully operated animals. The incisors of the latter were about two-thirds the size of those of the controls. The rate of eruption was promptly (within a week) and progressively retarded until there was cessation of eruption. Replacement therapy accelerated eruption if treatment was begun early. In the advanced stages after the hypophysectomy the tooth was practically solid and the enamel epithelium was lacking in the anterior eight- or nine-tenths of the incisor. In the remaining posterior portion the labial contour was distorted and presented multiple narrow and deep foldings and the enamel epithelium was markedly reduced. The cementum was considerably thickened. The pulp, the periodontal membrane, the labial alveolar periosteum, and Hertwig's sheath showed regressive changes.—Authors' Abst.

Excessive anterior-pituitary-like hormone and variations in oestrin in the toxemias of late pregnancy. Smith, G. V. S. and O. W. Smith, Proc. Soc. Exper. Biol. & Med. **30:** 918. 1933.

Quantitative determinations of the gonad-stimulating hormone and of oestrin have been made on the sera and urines of 27 women during late pregnancy, i.e., from 7½ months to term. The Aschheim-Zondek and Allen-Doisy methods have been employed. Ten cases were normal, 14 were diagnosed toxemia without convulsions and 3 had eclampsia. In every instance the serum and 24-hour urine of toxemic and eclamptic patients contained much more of the gonadotropic hormone than any of the normals. The average amount of serum required to give a positive Aschheim-Zondek test for the normal women was 2.05 cc., while that for the toxemics was 0.51 cc. The average urinary excretion of the normal women was 540 r. u. in 24 hours, while that of the toxemics was 4216 r. u. The amount of oestrin in the blood and urine of only 4 of the toxemic patients lay within normal limits. Nine of the remaining 10 showed less than that found in any of the normal controls. The average urinary excretion of oestrin for normal women was 6000 r. u., while that of the toxemics was 3800 r. u. in 24 hours. It is concluded that the blood and urine of toxemic and eclamptic patients in late pregnancy contain excessive amounts of the anterior-pituitary-like hormone, and wide variations in oestrin, with a decided tendency toward low levels. Preliminary experiments with hypophysectomized rats indicate that the excessive gonadotropic hormone of these toxemias may be hypophyseal in origin.—Authors' Abst.

Pituitary hormone intermedin, as the active antidiuretic in treatment of diabetes insipidus. Sulzberger, Marion B., J. A. M. A. **100:** 1928. 1933. Abst., A. M. A.

The work of Zondek and his collaborators led the author to believe that Intermedin might be the active principle in the treatment of diabetes insipidus and that the posterior pituitary solutions now in use were, perhaps, efficacious to some extent because of their Intermedin content. The Intermedin preparation was tested for possible harmful effects by Schwartz when he injected 1 cc. of it intravenously in himself. There were no ill effects or effects due to the administration of solution of posterior pituitary. The author reports the cases of two patients suffering from typical diabetes insipidus who were treated by Intermedin. In these two patients Intermedin had a marked effect in reducing both intake and output of fluid and thus alleviated the symptoms. The author

points out that although the observations have been restricted thus far to only two cases, it seems significant not only that the effects achieved were striking but that they were proportional to the quantity of Intermedin administered (in one patient, 1 cc., two and a half hours without urinating; 2 cc., five hours without urinating; in the other patient, 4 cc., fourteen hours without urinating). The author concludes that should Intermedin prove to be a specific hormone, regulating water metabolism; render diabetes insipidus patients comfortable for long periods of time, and, perhaps, even achieve some curative effect by aiding certain tissues to recuperate, and if the beneficial effect of solution of posterior pituitary in diabetes insipidus be due to its Intermedin content then other conditions which are today to some degree benefited by solution of posterior pituitary might be even more favorably influenced by the increased dosage made possible by the administration of pure Intermedin.

Effect of testicular hormone on hypophysectomized rats. Walsh, E. L., W. K. Cuyler and D. R. McCullagh, Proc. Soc. Exper. Biol. & Med. **30**: 848. 1933.

Hypophysectomized male rats were treated with testicular hormone extracted from urine. The testes, prostate glands and seminal vesicles maintained in normal weight and histological appearance.—M. O. L.

The influence of hypophysectomy on the blood sugar and glucose tolerance in Xenopus laevis. Zwarenstein, H. and L. P. Bosman, Quart. J. Exper. Physiol. **22**: 45. 1932.

The authors found that the color of the background, although influencing color changes through the pituitary, was without influence on the fasting blood sugar. Hypophysectomy, whether total or partial, had no effect on the fasting blood sugar. In 19 animals hypophysectomized 5-6 months previously, the injection of glucose caused much less rise in blood sugar taken 30 minutes after injection than in a similar number of controls. They conclude that hypophysectomy results in a greater tolerance for glucose in this species.—B. O. Barnes.

Diabetes mellitus of syphilitic origin. Brandau, G. M., Am. J. Syphilis, **16**: 511. 1932.

This paper gives a brief resume of the literature discussing the relationship of diabetes and syphilis, and outlines the postulates that have been set up as criteria in the diagnosis of syphilitic diabetes. Cases reported since 1929 are briefly outlined. The case was reported of a woman 51 years of age with diabetes and syphilis. Laboratory tests disclosed glycosuria, blood sugar 363 mg. per 100 cc. of blood and four plus Wassermann reaction. The diabetes was after a time brought under control by restriction of diet and 40 units of insulin per diem. Antisyphilitic therapy was begun, but after a few injections of bismuth the patient ceased to report for treatment. Four months later she returned. She had discontinued the insulin and had ceased weighing her food. The Wassermann was four plus and the blood sugar, two hours after the principal meal, was 177 mg. per 100 cc. of blood. The urine was sugar-free. The anti-syphilitic regime was resumed and in October the Wassermann was negative, the Kahn four plus. On November 4, 1931, the blood sugar was 88 mg. At this time the patient was not taking insulin and did not weigh the diet, although she exercised some restriction in starch food. In May, 1932, she continued in good health. It was concluded that in occasional cases of coexistent diabetes and syphilis antisyphilitic therapy results in remarkable improvement or cure. Diabetics in whom syphilis is proved or suspected should be given the benefit of antisyphilitic treatment for its possible good effect on the diabetes as well as for its general antisyphilitic value. Cases of coexistent diabetes and syphilis in which, subsequent to the establishment of a glycoregulatory balance, the therapeutic test with antisyphilitic treatment is undoubtedly positive in its effect on the diabetes, should be considered as cases of syphilitic diabetes. A possible exception may be found in diabetes associated with florid syphilis. In cases of coexistent diabetes and syphilis in which, subsequent to the establishment of a glycoregulatory balance, the therapeutic test with antisyphilitic treatment is negative in its effect on the diabetes, the association of the two diseases should be regarded as incidental until further evidence is adduced.
—Author's Abst.

On the different degrees of activity of insulin injections in rabbits according to the route used (Sur les différences d'activite des injections d'insuline chez le lapin suivant la voie d'administration). Chevillot, M., J. Harmand, L. Hennequin and M. Lambert, Compt. rend. Soc. de biol. **112**: 65. 1933.

Regardless of the size of the dose, the hypoglycemia is less marked and more rapid in development and disappearance when the insulin is given intravenously. When the insulin is poured directly into the blood stream, it is dissipated before it has time to act very extensively on the liver.—J. C. D.

The effect of infection on the insulin content of the pancreas. Murray, D. W. G. and E. T. Waters, Tr. Roy. Soc. Canad. **26**: 169. 1932.

In eight dogs with peritonitis it was found that the insulin content of the pancreas was significantly lower than that of eight controls (roughly about 20%, depending upon the severity of the infection). The assays were made on white mice (20 or more, starved 5-7 hours before the tests).—R. G. H.

Uterine motility in hypophysectomized and in pregnant rabbits. Reynolds, S. R. M. and W. M. Firor, Am. J. Physiol. **104**: 331. 1933.

In rabbits hypophysectomized on the fifth to sixth day of pregnancy or pseudopregnancy, the corpora lutea lost within 48 hours their power to inhibit typical uterine contractions induced by oestrin (Theelin; six experimental, one control rabbit). In eight unanesthetized pregnant rabbits the uterus was refractory to the motility-inducing action of Theelin until the twenty-sixth day of pregnancy, but on the twenty-seventh day the injection of Theelin led to abortion and death. In seven rabbits it appeared that the corpus luteum functions at a high level, as regards maintaining uterine quiescence, until about the middle of the fourth week of gestation, and is no longer functioning in this regard by the end of the fourth week.—R. G. H.

Demonstration of the true hormonal character of vagotonine and of its properties (Démonstration du caractère veritablement hormonal de la vagatonine et de ses propriétès). Santenoise, F., Y. Porc'her and M. Vidacovitch, Compt. rend. Soc. de biol. **112**: 67. 1933.

Vagotonine is extracted from the pancreas as the result of a specific method. It gives definite chemical reactions. It has definite effects on the oculo-cardiac reflex, the reflex of Cyon, the reflex of Hering, the curve of summation, and the vagus reflex centers in dogs. Ablation of the pancreas reduces these actions and injections of vagotonine or of blood from the pancreatic vein re-establishes them. Vagotonine, therefore, fulfills the requirements laid down by Gley for the recognition of a true hormone.—J. C. D.

Observations on insulin crystals. Scott, D. A., Tr. Roy. Soc. Canad. **26**: 275. 1932.

A technical study of insulin from the crystallographic point of view. It was found that the substance will crystallize in two definite crystal habits at different acidities. Since both have the same physiological activity it is believed that crystalline insulin is a definite chemical entity. The technical aspects of the article do not lend themselves to abstracting.—R. G. H.

The prediabetic state; its relation to obesity and to diabetic heredity. Tyner, J. D., Am. J. M. Sc. **185**: 704. 1933.

A series of 500 normal and 500 prediabetic carbohydrate tolerance tests were analyzed to determine the incidence of obesity and diabetic heredity in the prediabetic state. Body weight cannot be correlated with the prediabetic state. Obesity does not present an increased incidence, nor underweight a decreased incidence of prediabetes; each is equally associated with it. Prediabetes is correlated, in general, with age. The peak is reached in the seventh decade and thereafter declines. Sex does not appear to be a factor in prediabetes. Heredity of the direct diabetic type shows an increased incidence of prediabetes in the obese, not in the thin. Heredity of the familial type is not associated with prediabetes any more than the average group of cases.
—Author's Abst.

Diabetes mellitus and myxedema. Weinstein, A., Bull. Johns Hopkins Hosp. **51**: 27. 1932.

The literature contains but 10 instances of the unusual combination of diabetes mellitus and myxedema. These cases are reviewed and two additional added. In one of these latter autopsy findings were available and the pathological specimens confirmed the clinical impression. Both of these patients had an accentuation of the evidences of diabetes when thyroid extract was given to combat the lack of thyroid secretion. The various experimental data and theoretical possibilities are discussed, but there is no satisfactory explanation of this phenomenon.—Author's Abst.

Changes in the bone marrow in hens treated with parathyroid hormone (Modifications de la moelle osseuse chez la Poule traitée par l'hormone parathyroïdienne). Parhon, C. I. and C. Parhon-Stefanescu, Compt. rend. Soc. de biol. **109**: 903. 1932.

A young hen received 10 units of parathormone daily for two weeks. The bone marrow showed marked increase in fat, while myelocytes almost disappeared in contrast with the control.—J. C. D.

The parathyroid hormone; its regulatory action on the parathyroid glands and toxic effect on the tissues of the rat. McJunkin, F. A., W. R. Tweedy and H. C. Breuhaus, Arch. Path. **14**: 649. 1932.

Injections of parathyroid hormone into half-grown rats diminished the proliferative activity of the parathyroid gland cells. This inhibiting effect of the hormone was accomplished by small doses insufficient to produce hypercalcemia and destructive lesions of parenchymal organs. An inactivated hormone, completely inert as determined by the usual method for testing activity, arrests parathyroid proliferation, but produces neither hypercalcemia nor destructive lesions. These effects were determined by counting all mitoses in the parathyroid glands of the animal. For accurate enumeration it was necessary to fix the tissue by a special technic for embedding in paraffin and serial sectioning. The inhibiting effect of the hormone on the growth of the gland was regarded as a manifestation of a self-regulatory mechanism probably present in various glands since thyroglobin, insulin, and epinephrin were found to inhibit karyokinetic activity of the tissues producing those hormones. The lesions produced by excessive doses of the hormone are toxic and primary. The circulatory failure which characterizes the fatal cases is secondary to the destructive lesions in the myocardium. To demonstrate this a kidney was removed 24 hours after a single large dose of parathyroid hormone at a time when circulatory disturbance was not demonstrable and in it foci of necroses had already appeared. At the end of 48 hours the remaining kidney revealed later stages of the necrosis with calcification and at this time signs of circulatory failure were present. Our experiments did not clearly determine the mechanism responsible for the destructive tissue lesions.—F. A. McJunkin.

Effect of thyroparathyroidectomy and of thyroid feeding in rats on limited intake of vitamin B. Templeton, R. D. and Mary C. Patras, Proc. Am. Physiol. Soc. P. 95. 1933.

Three groups of rats, litter mates, aged 150 to 200 days, were placed on a diet consisting of starch, 57%; casein, 18; unsalted butter, 15; salt mixture (Osborne and Mendel), 3; cod liver oil, 2, and fresh bakers' yeast, 5%. This quantity of the yeast preparation used is inadequate for the prevention of polyneuritic symptoms. Group A (13 rats) were thyroparathyroidectomized on the 17th day of the experiment. Group B (14 rats) from the 30th day, received desiccated thyroid, 0.05% added daily to the diet. Group C (14 rats) were continued as controls. All rats of Group A died between the 63rd and 94th days from the beginning of the diet, the average survival being 81.3 days. For Group B the survival range was from 57 to 75 days, average 67.5; for Group C, 59 to 80 days, average 67.5. The difference between Group B and the controls is perhaps too small to be of significance. The resistance to vitamin B deficiency, however, appears to be definitely increased in the animals with thyroids and parathyroids removed.—Authors' Abst.

Cornification and molting in Triturus. Adams, A. Elizabeth and Margaret C. Grierson, Proc. Soc. Exper. Biol. & Med. **30**: 341. 1932.

The rate of cornification of the superficial epidermis of Triturus is markedly variable and probably independent of thyroid control, but the molting of the cornified layers is dependent on the thyroid. Experiments indicate that a change in cutaneous circulatory conditions is probably an essential factor in the molting mechanism.—Authors' Summary.

Excretion of iodine in experimental hyperthyroidism. Barnes, B. O., Am. J. Physiol. **103**: 699. 1933.

Iodine excretion was determined in 29 dogs after administration of desiccated thyroid, thyroglobulin, or thyroxine. With the two former preparations about 50% of the iodine was eliminated through the urine, while very little appeared in the bile. After intravenous thyroxine administration a greater proportion of the injected iodine appeared in the bile than in the urine. After the intravenous injection of thyroxine, about half of the iodine was excreted before the rise in basal metabolism occurred. Since very little iodine appeared in the bile after feeding large doses of desiccated thyroid, it is concluded that free thyroxine is not liberated.—B. O. Barnes.

The feather germ test for thyroid hormone. Barnes, B. O., Proc. Am. Physiol. Soc. P. 3. 1933.

In the routine use of brown leghorn capons for detecting the thyroid hormone, the birds are injected once in three weeks. At the time of injection a few feathers are plucked from the saddle region. New feathers grow in and are about the proper age in 3 weeks. Four regions in the saddle area are used in rotation, the front and back portion on either side. Three days after the injection has been found the most satisfactory time to examine the young feathers. If a sufficiently large dose of thyroid hormone has been administered, a black line can be seen at the base of the germ. The threshold dose of thyroxine for a group of 60 capons was determined by injecting decreasing quantities. All birds gave a positive response on doses of 0.4 mg. or more of thyroxine. About 50% responded to 0.2 mg. Tests are being made to see if the reaction can be used quantitatively.—Author's Abst.

Further studies on the excretion of iodine in experimental hyperthyroidism. Barnes, B. O. and T. H. Chang, Proc. Am. Physiol. Soc. P. 3. 1933.

In a previous study it was shown that after feeding desiccated thyroid, about half of the iodine was excreted in the urine while very little was present in the bile. On the other hand, when thyroxine was injected, a greater proportion of the iodine was excreted in the bile, although some was present in the urine. Leland and Foster showed that thyroxine could be extracted by butyl alcohol. We have applied this method to urine after feeding desiccated thyroids or injecting thyroxine and have found very little thyroxine in the urine. Extraction of bile collected after injecting thyroxine yielded about two-thirds of the iodine in the butyl alcohol. We have found that when thyroglobulin is injected intravenously, some of the iodine is excreted in the urine while very little comes out through the bile. Splitting thyroglobulin into acid-soluble and acid-insoluble fractions and testing these fractions for iodine excretion after oral administration, it was found that a much greater percentage of the iodine in the acid-soluble fraction comes out in the urine than when the acid-insoluble fraction is administered.—Authors' Abst.

Mineral metabolism during involution of simple goiter. Bauman, E. J., Sarah Kurland and Nannette Metzger, J. Biol. Chem. **94**: 383. 1931.

The relation of mineral metabolism of rabbits to the physiological state of the thyroid was examined. In thyroid deficiency (caused by feeding rabbits with winter cabbage until a palpable goiter was produced) there was found a retention of calcium, magnesium and phosphorus of about 0.4, 0.1 and 0.3 gm., respectively, per 3-day period. Converting the thyroid to the normal colloid-containing state by giving 10 mg. KI restored the balance of these elements by increasing the amounts excreted. The metabolism of sodium, potassium, chlorine and sulphur was relatively uninfluenced by thyroid deficiency. A mineral balance experiment on rabbits on a diet of alfalfa and oats is given for comparison,—Authors' Abst.

Changes in the excitability of the sympathetic nervous system through thyroxine (Erregbarkeitsänderung des Sympathicus durch Thyroxin). Bergwall, A. and G. Kuschinsky, Arch. f. exper. Path. u. Pharmakol. **162:** 167. 1931.

The authors use the normal iris and the denervated iris for their test, determining the dilating dose of adrenaline. They found that insulin had no effect on the excitability directly but might have an influence through the adrenals. The excitability was increased during thyroxine administration even in cases of the denervated and atropinized iris from which the authors conclude that thyroxine has a peripheral point of attack.—B. O. Barnes.

Postoperative Graves' disease. Bram, I., Northwest Med. **31:** 526. 1932.

This is a brief review of the author's experience with postoperative subjects of Graves' disease who nevertheless present evidences of the syndrome in varying degree. Out of a total series of nearly 4300 cases of Graves' disease seen by Bram during a period of over 20 years, 562 or approximately 13% were in patients who had undergone one or more thyroidectomies. Postoperative Graves' disease may occur in the following forms: (a) persistence in varying degree of the original syndrome without an intervening period of apparent normality; (b) recurrence of symptoms after weeks, months or years of apparent normality; (c) the existence in combination of so-called hypothyroidism and hyperthyroidism with or without a brief period of apparent well-being immediately following thyroidectomy; (d) persistence or recurrence of Graves' symptoms with a complicating acromegaly, and (e) persistence of Graves' syndrome with the superimposition of a major psychosis, usually in the form of manic-depressive insanity. From these observations it would appear that Graves' disease is not synonymous with hyperthyroidism nor is it primarily a disease of the thyroid. In the treatment of a syndrome the etiology of which is still unknown, it would also appear that the clinical habit of taking thyroidectomy for granted as the logical therapeutic measure calls for reconsideration.—Author's Abst.

Studies in cretinism and hypothyroidism in childhood; blood cholesterol. Bronstein, I. P., J. A. M. A. **100:** 1661. 1933. Abst., A. M. A.

The author points out that a review of the literature indicates that a relationship exists between hypercholesteremia and hypothyroidism in adults. He tried to ascertain the presence of a similar relationship in hypothyroidism of children. He determined the blood cholesterol in 25 children in whom no known derangement of cholesterol metabolism was present, and the average was found to be 190 plus. This value for normal cholesterol is substantiated by the work of other investigators in this field. Hypercholesteremia was found in the 12 thyroid deficient children studied. The values ranged from 277 to 782. Thyroid therapy definitely lowered the blood cholesterol in the cases cited, in addition to raising the basal metabolic rate and effecting clinical improvement. It is desirable to have an additional method for the diagnosis and treatment of thyroid deficient children, particularly in infants and borderline cases. The author believes that the use of cholesterol as an aid in the diagnosis and regulation of thyroid dosage offers definite possibilities.

The effect of feeding thyroid on the salivary conditioned reflex induced by morphine. Crisler, G., W. T. Booher, E. J. Van Liere and J. C. Hall, Am. J. Physiol. **103:** 68. 1933.

In 11 dogs daily doses of 2½-3 gm. decissated thyroid tissue by mouth at first enhanced and then depressed the conditioned secretion of saliva (tested for ½ hour daily) caused by morphine injections into dogs with salivary fistulae, when the diet remained constant and water was given ad lib. Unconditioned salivary secretion remained unchanged. The stimulation of conditioned secretion—which did not last for longer than three days—was probably a reflection of cerebral stimulation by the extract. The subsequent depression that was observed represented the later tissue dehydration, in contra-distinction to blood volume changes, by the thyroid. It was concluded that the mechanism is central and not peripheral as indicated by the unchanged unconditioned secretion.—R. G. H.

Blood flow through the thyroid (Untersuchungen über die Schilddrüsendurchblutung). Dietrich, S. and H. Schwiegk, Arch. f. exper. Path. u. Pharmakol. **165**: 53. 1932. Abst., Physiol. Absts. **17**: 744.

The rate of blood flow through the thyroid and its consumption of oxygen have been determined in various conditions. Under light anaesthesia both are increased by cooling the animal and diminished by warming it; under deeper anaesthesia these effects are no longer obtained. Artificial fever by injection of bacterial toxins does not affect the thyroid, but both blood flow and oxygen consumption are increased several hundreds per cent by the fever induced by injection of tetrahydro-beta-naphthylamine. Adrenaline, ergotamine, and hypophysein diminish the blood flow, and histamine, pilocarpine and peptone increase it.

Thyroxine and arginine metabolism (Zur Kenntnis der Arginasewirkung; Thyroxin und Argininstoffwechsel). Edlbacher, S. and B. Schuler, Ztschr. f. physiol. Chem. **206**: 78. 1932. Absts. **26**: 3524.

Subcutaneous injection of arginine in guinea pigs results in a four-fold increase in the arginase value of the musculature. This increase is also evident in the kidney. The maximum is reached in about five hours. If a thyroxine injection is given one hour before the arginine treatment, the aginase increase does not occur. This is interpreted as an oxidative destruction of the arginine under the influence of thyroxine. In the surviving cat liver perfused with erythrocytes in Ringer's solution and sufficient oxygen, the arginine cleavage into urea and orinthine is only 60-70% as great in the presence as in the absence of thyroxine. There is evidently an antagonistic influence of thyroxine on arginase action. These observations confirm the hypothesis of combined oxidative and hydrolytic processes in metabolism, such as is known in carbohydrate metabolism as the Pasteur-Meyerhof reaction.

Ultraviolet light and goiter (Ultraviolettes Licht und Kropf). von Fellenberg, T., Biochem. Ztschr. **235**: 205. 1931.

Two groups of white rats were exposed to the sunlight of high altitudes, namely, at Davos, 1560 m., and at Muottas Muraigl, 2456 m. The iodine content of the thyroid glands were determined after a few weeks and compared with the figures obtained from the control groups which had been kept in darkness. The average iodine value per gram of gland tissue for the Davos "dark" group was 40 gamma, while that of the Davos "light" groups was 36 gamma. At Muottas Muraigl the "light" group tended to have a higher value for iodine than did the "dark" group, but this series (2 and 3 cases) was too limited to be significant. In addition, air, water and milk from localities of different altitudes, chiefly Bern 540 m. and Davos, were analyzed for iodine. Although the iodine value of the atmosphere decreased as altitude increased, the author obtained no evidence for a difference in the iodine supply of Bern and Davos. The prevalence of goiter was definitely related to the iodine deficiency of the environment, especially water. Consequently no evidence was found to support the histological findings of Bergfeld which indicated that ultraviolet irradiation may have a beneficial influence on goiter. A possible explanation of the conflicting results was offered based on the fact that in the latter's experiments all rays longer than 310 μμ were eliminated by filtration.

—Caroline tum Suden.

Assay of thyroid by chemical estimation of the thyroxine content. Gutman, A. B., E. M. Benedict and W. W. Palmer, Proc. Soc. Exper. Biol. & Med. **29**: 1198. 1932.

Fifteen commercial thyroid preparations were analyzed for total iodine by a modified Kendall method, inorganic iodine by aqueous extraction and thyroxine by the Leland and Foster method. The content of thyroxine iodine varied from 0.0099 to 0.0355 mg. per one grain tablet, the mean discrepancy between duplicates being 2.7%. The variation indicated is consistent with results obtained by many authors by biological assay and by Kendall's acid precipitation method. The variation in thyroxine content was much less in those preparations which satisfied U. S. P. requirements. It is suggested that standardization of thyroid preparations according to thyroxine content as determined by Leland and Foster's method could reduce this variation to a satisfactory minimum and detect adulteration with physiologically inactive iodine compounds.—A. B. Gutman.

Effects of decerebration on the thyroid (Osservazioni sperimentali sulla tiroide nelle lesioni cerebrali). Jedlowski, P., Boll. d. Soc. ital. di biol. sper. **7**: 55. 1932. Abst., Physiol. Absts. **18**: 135.

The thyroid was studied after death in four decerebrate hens. It was found to be more than twice the normal size and contained large follicles with greatly hypertrophied epithelia.

The management of severe and of atypical hyperthyroidism. Lahey, F. H., Ann. Int. Med. **5**: 1123. 1932.

A very large percentage of patients who are permitted to get into the advanced state of thyroid crisis will die. Their salvation is the early detection of an impending thyroid crisis or undue intensification of their hyperthyroidism and its emergency treatment with iodine, morphine, amytal, avertin, salt solution and glucose. By the early application of these measures, patients may be kept out of thyroid crises, prepared and operated on by subtotal thyroidectomy within three weeks and definitely relieved of their thyroidism. Apathetic hyperthyroidism is a state characterized by signs and symptoms quite contrary to those of typical activated hyperthyroidism. It is misleading not only as to its existence but it is also misleading as to its seriousness, and possesses graver dangers of a fatality under stress of operative procedure than does the typical activated hyperthyroidism. An appreciation of its atypical signs and symptoms will result in early diagnosis and an appreciation of its certain unobtrusive seriousness should make one realize the possibilities of a fatality when the patient is submitted to any considerable extra burden, particularly such as subtotal thyroidectomy in one stage. It should make one undertake surgical procedures in two stages, in all patients of this type, no matter how good they appear as risks.—I. B.

The blood picture in exophthalmic goiter and its changes resulting from iodine and operation. Hertz, S. and J. Lerman, J. Clin. Investigation, **11**: 1179. 1932 .

By means of the method described by Sabin for supravital blood examination the blood pictures of 30 untreated patients with exophthalmic goiter were studied. The effect of rest, iodinization and operation on the blood picture was observed in 18 cases. It was found that this method made possible better differentiation of the large lymphocyte, monocyte and monolobed granulocyte than did the fixed smear. Leukopenia, hypopolyneuclosis, slight relative lymphocytosis and marked relative and absolute mononucleosis were found to be quite characteristic of exophthalmic goiter. No correlation existed between the height of the leukocyte count and the basal metabolic rate. The percentage of polymorphonuclear cells show a direct correlation with the height of the metabolic rate, while the percentage of lymphocytes showed an inverse relationship. The percentage of monocytes tended to vary with the height of the metabolic rate. In general iodinization caused a decrease in the total white blood cells, a slight increase in polymorphonuclear cells and a slight decrease in lymphocytes. The most constant effect was a decrease in percentage and absolute number of monocytes. Operation per se caused very little permanent change in the blood picture. There was a rise in the total white blood cells immediately after operation. The polymorphonuclear cells and monocytes were both temporarily increased at that time. The elevated monocyte count and its depression by iodine were interpreted in the light of Aschoff's theory of the origin of the monocyte as evidence for an activated reticulo-endothelial system in exophthalmic goiter and for a depression of that system in the course of the remission produced by iodine.—Authors' Abst.

On the liberation of iodine from thyroid gland extract (suspension by quartz-lamp irradiation as well as from iodized protein by Röntgenation) (Über die Abscheidung von Jod aus Schilddrüsenbrei durch Quartzlampenbestrahlung sowie aus Joseiweiss durch Röntgenstrahlung). Lieben, F. and H. Kraus, Biochem. Ztschr. **236**: 182. 1931.

Continuing previous work on the liberation of I_2 from irradiated iodized protein the authors investigated the effect of ultra-violet light on human thyroidbrei. The glands were obtained from seven subjects at autopsy. A 4 mm. deep suspension in iced Ringer's solution of each specimen was irradiated for 2 hours at a distance of 15 cm. from a Heraeus quartz-mercury-vapor lamp

(220 volts, d.c., 2000 candle power). The iodine content of the water dialysate was determined by the titration method of Fresenius. The yield was definite but minute in all seven cases, ranging from 0.5 to 2.7% of the total iodine content of the gland. A yield of 1% was obtained after Röntgenation of iodized casein or thyroxin as substrate.—Caroline tum Suden.

The glutathione in the blood of hyperthyroid cases (Le glutathion intrahématique chez les hyperthyroïdiens). Litarczek, G., H. Aubert and B. Nestoresco.

Certain ideas on the respiratory exchange in hyperthyroid cases. Conception of the pathological process (Quelques données sur les échanges respiratoires chez les hyperthyroïdiens. Conception pathogénique). Litarczek, G., H. Aubert and J. Cosmulesco, Compt. rend. Soc. de biol. **112:** 82; 84. 1933.

Glutathione was somewhat reduced in the blood of 8 hyperthyroid cases. The loss of oxygen to the tissues as shown by the oxygen content of arterial and venous peripheral blood was reduced in three cases examined. Both these facts suggest that the greater metabolic rate in hyperthyroid condition is a secondary result of the more active circulation and not of an increased oxygen hunger of the tissues.—J. C. D.

Effect of sodium bromide on thyroid gland of the guinea pig. Margolin, E. S., Proc. Soc. Exper. Biol. & Med. **30:** 495. 1933.

Administration of sodium bromide to 37 guinea pigs caused increases in the number of mitoses in the thyroid acini which were statistically significant. There was also a softening of the colloid and an increase in the size of the acinar cells. It is concluded that bromide in the form of NaBr exerts a definite stimulating effect on the mammalian thyroid. The effect was only about one-fifth as great as that produced by iodine.—M. O. L.

Iodized table salt and goiter surgery in Detroit. McClure, R. D., Wisconsin M. J. **31:** 519. 1932.

This paper presents data tending to show a marked decrease in both the toxic diffuse and the nodular goiters in the Detroit area since iodized salt was introduced into Michigan in 1925. The conclusions are based on figures from three of the large hospitals of Detroit, and from the University Hospital at Ann Arbor. Although there was an increase in total number of operations, there was a marked decrease in total number of thyroidectomies. Likewise, there has been a decrease of incidence of non-toxic diffuse goiter in Detroit school children, from 35% in 1924 to 2.1% in 1931. It was felt that reported instances of ill effects from the use of iodine salt were not based on sound observations. The conclusions arrived at were that: first, there has been a tremendous reduction in the incidence of non-toxic diffuse goiter in the Detroit area since the introduction of iodized salt; second, there has, likewise, been a great decrease in the number of operations for goiter; and third, while it is not concluded that iodine deficiency is the only cause of goiter, it is felt that if the thyroid gland can be kept in its normal state by a sufficient iodine intake, goiter is less apt to develop.—Author's Abst.

The influence of thyroxine on the avertin concentration of the blood (Über den Einfluss des Thyroxins auf die Avertinkonzentration im Blut). Nell, W., Klin. Kchnschr. **11:** 367. 1932.

The dosage of avertin varied from 0.1 to 0.125 gram per kilo of body weight. The avertin concentration in the blood was determined at the end of 20, 30, 60 and 120 minutes. The duration of anesthesia produced was also recorded. In 20 control cases, the avertin concentration of the blood reached the maximum, 7 mg. % in 30 minutes, and the average duration of anesthesia was 2.5 hr. With 20 cases in which 0.2 mg. of thyroxine was administered intravenously ½ hr. after anesthesia and in 17 cases in which 0.2 mg. of thyroxine was administered 1 hr. before anesthesia, the results were similar to the control cases. In 22 cases in which the basal metabolism was increased by previous thyroxine administration for several days the average of the maximum avertin concentrations was about 4.2 mg. % and the duration of anesthesia, 1.5 hr. The maximum concentration of avertin was reached at the same time but the rate of decrease in the patients with increased basal metab-

olism was less. In 6 patients who received sufficient thyroxine to cause toxic symptoms and a decided increase in the B.M.R., there was a maximum average concentration of avertin in the blood of 10.1 mg. % at the end of 30 minutes and the duration of anesthesia was 5.7 hr. These results in patients with toxic symptoms are similar to those produced in persons who are cachectic.
—E. L.

Effect of thyroparathyroidectomy on the lipids, fatty acids, cholesterol, and protein in the blood serum (Influence de la thyroparathyroïdectomie sur la teneur du sérum sanguin en lipides, acides gras, cholestérol et protides). Parhon, C. I. and I. Ornstein, Compt. rend. Soc. de biol. **109:** 901. 1932.

Complete examination of 9 dogs before and within a week after operation showed in most cases an increase in all these constituents following thyroparathyroidectomy.—J. C. D.

The folliculin-like action of a lipoid isolated from bacillus tuberculosis (De l'action folliculinique d'un lipoide isolé des Bacilles tuberculeux). Pedersen-Bjergaard, K., Compt. rend. Soc. de biol. **112:** 103. 1933.

One thousand grams of dried tubercle bacilli contain about 250 mouse units of a lipoid which gives prolonged active oestrus in castrated mice.—J. C. D.

Surgical operations and associated infections as possible etiological factors in the development of exophthalmic goiter and of hyperthyroidism from adenomatous goiter. Plummer, W. A. and C. Mayo, Surg. Gynec. & Obst. **53:** 721. 1931.

In cases of exophthalmic goiter or hyperthyroidism from adenomatous goiter, in which the onset of symptoms was attributed to acute infection, nervous shock, or operation, the disease was probably present before the acute infection, nervous shock, or operation. In the isolated cases in which the time of onset of the toxic symptoms of goiter coincides approximately with some major operation not of the thyroid gland, the relationship may be coincidental. Even in cases of exophthalmic goiter, a disease which many observers believe is based on constitutional predisposition, major operations and their associated factors, such as acute and chronic infectious processes, fear, and trauma, do not usually precipitate the disease. In spite of the infrequency of cases in which the development of exophthalmic goiter and of hyperthyroidism from adenomatous goiter approximately coincides with that of some major operation not related to the thyroid gland, and admitting the possibility of coincidental relationship, the authors believe that the evidence obtained in the cases so far studied tends to support the contention that acute or chronic infectious processes are precipitating or aggravating factors in the development of exophthalmic goiter or of hyperthyroidism from adenomatous goiter if persons are predisposed to these diseases. That infectious processes, in the etiology of exophthalmic goiter, affect the thyroid gland specifically or directly has never been proved. It is probably the consensus of opinion that they play an etiologic rôle only in certain cases, and then by lowering the resistance of the patient by exerting some unusual stimulation on the thyroid gland, or in some other indirect, non-specific manner.—I. B.

Iodine resistant hyperthyroidism. Potter, E. B. and W. R. Morris, West. J. Surg. **40:** 544. 1932.

A study was made from the end results in 700 thyroidectomies with reference to those goiter patients who failed to respond to the preoperative administration of iodine. The casese were divided into three groups: (1) Exophthalmic goiter, (2) toxic adenoma, and (3) colloid goiter. The majority of cases of resistance to iodine were in those with a basal metabolism of +50% and above. Of the exophthalmic group of 267 subjects, 31 or 11.6% failed to respond to the administration of Lugol's solution; 38% of these had taken iodine in some form prior to hospitalization. In 273 patients with toxic adenomas, 10 or 3.6% were refractory to a preoperative course of iodine, although it was shown by a previous study that one-half of this group could not be expected to react favorably to iodine because of important histo-pathological differences. Reference to the colloid goiter group included two illustrative cases with all of the clinical criteria of severe exophthalmic goiter and a pathological picture of simple colloid goiter. The prolonged use of iodine seemed to

be responsible for the production of an iodine resistant state in 40% of the entire group, while in 60% of patients refractory to iodine, the only known source of iodine was iodized table salt. The proven benefits of iodized salt in goiterous regions, however, justifies its use and the suggestion was made that some unrecognized factors, other than the activity of the thyroid gland, are concerned in the production of the iodine resistant state. Fractional operations (performed in about 50% of the entire group) provide the safest method of dealing with the iodine resistant thyroid.—E. B. Potter.

Occurrence of a calcareous arterial lesion in goiter. Pusch, L. C., Arch. Path. **14**: 353. 1932.

An arterial lesion characterized by hyalinization, fragmentation and calcification of the elastica interna was found in 56 goitrous thyroid glands of 100 consecutive partial thyroidectomies. No significant relationship of the lesion to type of goiter, structure of the thyroid gland, hyperthyroidism, iodine therapy, duration of goiter, presence of concomitant disease, age of patient, or to blood pressure was manifest. Imperceptible gradations in degree of involvement suggested a development of the lesion from a thin, barely perceptible, thread-like, hyaline or calcareous band to bulky calcareous deposits occupying most of the thickness of the arterial wall, when it conformed morphologically with Monckeberg's medical calcification of peripheral arteries. Slight to moderate degrees of intimal fibrillar proliferation and medial hypertrophy were associated with the lesion, but typical arteriosclerotic intimal plaques were not observed. The lesion occurred in 3 of 25 normal thyroid glands removed at autopsy, but was not observed in other tissues in these cases. It was not found in 50 thyroid glands of fetuses and new-born infants. The significance of the lesion was not manifest.—Author's Abst.

Malignant hypertensive vascular disease simulating hyperthyroidism; clinical course following maximal subtotal thyroidectomy. Rose, E., M. Clin. North America, **16**: 261. 1932.

This is a review of a phase in the diagnosis of hyperthyroidism that is occasionally overlooked, namely, the confusion of this syndrome with the symptoms of malignant hypertension. The author reports a case which occurred in a single woman of 36. Malignant hypertension occasionally presents a clinical picture which can with difficulty be differentiated from that of thyroid hypersecretion. Rapid heart, a moderately increased basal metabolic rate, vascular throbbing, more particularly at the neck, weakness and loss of weight are symptoms common to both conditions. However, in hypertension there is little, if any, response to iodine medication, radiation, or maximal resection of the thyroid.—I. B.

Nitrile cleavage and its modification by thyroid preparations (Einige Untersuchungen zur Frage der Nitrilspaltung im tierischen Organismus and deren Beeinflussung durch Schildrusenpräparate bzw. Thyroxin). Schechter, M., Ztschr. f. klin. med. **117**: 660. 1931.

The author has confirmed and extended the earlier observations of Lang, Hunt and others that after the administration of acetonitril (methyl cyanide) to guinea-pigs and other animals there is an increased formation and excretion of thiocyanate; this was determined in the saliva, urine, and blood. It was found that the administration of thyroid increased the thiocyanate in the serum 100-200%; this is interpreted as showing that there is, under the influence of thyroid, an increased formation of hydrocyanic acid and that this is in harmony with the experiments of Hunt which showed that the administration of thyroid to guinea-pigs and rats lowered the resistance of these animals to the nitril. The author has no explanation to offer of the more interesting fact that the administration of thyroid greatly increases the resistance of white mice to acetonitril; this increased resistance in the case of mice is the basis of a method for detecting minute amounts of thyroid.—Reid Hunt.

Certain features of the etiology of goiter. Smith, J. H., Virginia M. Monthly, **60**: 90. 1933.

Two factors are considered as causes of goiter. In support of each proposition, experimental evidence as related to animals is quoted and statistical evi-

dence as related to man is presented. (1) Deficiency of solar radiation: Bergfeld's work with rats and McCarrison's work with goiter in rabbits, produced by feeding cabbage, are cited; Stott's observations in India and the author's study of his correlations as applied to India, New Zealand and South Carolina are mentioned, and data related to the United States are presented in some detail. (2) Depression of the rate of oxidation: Marine's work in producing goiter with exophthalmos in rabbits by injection of cyanide is cited; the author presents correlations which he believes to be significant between the ratio of simple goiter to exophthalmic goiter as reported by the United States Draft Board, and normal oxygen consumption as computed on the basis of mean temperatures and humidities for July, based in turn on the experimental observations of others as to the influence of these climatic factors. The conclusions reached with reference to the age and sex group studied (young men) are, that deficiency of solar radiation tends to an increased prevalence of endemic goiter; prevalence of simple goiter tends to prevalance of exophthalmic goiter; and the incidence of exophthalmic goiter is favored by conditions of temperature and humidity which tend under experimental conditions to decrease the rate of tissue oxidation.—Author's Abst.

Solar radiation in relation to endemic goiter. Smith, J. H., Arch. Int. Med. **50**: 76. 1932.

Data are presented as evidence that deficiency of solar radiation tends to simple or endemic goiter. The evidence consists of statistical data related to distribution and prevalence of goiter, and meteorological data related to solar radiation. The author believes that the correlations are significant. He points out also correlations between deficiency of solar radiation and deficiency of ioidine in soil and water. Geographically, the United States, India, New Zealand and South Carolina are considered. The conclusion reached with respect to each is the same; namely, that a deficiency of solar radiation tends to a deficiency of the iodine content of the thyroid gland due to a lack of irradiation of the air, soil, food, drinking water or the skin of the animal organism, tending to an increased prevalence of goiter.—Author's Abst.

The range of effective iodine dosage in exophthalmic goiter; the effect on basal metabolism of the daily administration of about 0.75 mg. of iodine. Thompson, W. O., Phebe K. Thompson and A. C. Cohen, Arch. Int. Med. **49**: 199. 1932.

During the daily administration of about 0.75 mg. of iodine in the form of the compound solution to 12 unselected hospital patients with exophthalmic goiter, four showed a reduction in basal metabolism of from 11 to 19 points, six showed no change and two showed an increase. Whereas only 33% of the patients showed a reduction in basal metabolism of 10 points or more during the daily administration of 0.75 mg., 50% showed a reduction during the daily administration of 1.5 mg., 65% during the daily administration of 3 mg. and 88% during the daily administration of 6 mg. The administration of about 0.75 mg. a day caused an average reduction in basal metabolism of 4 points (from plus 39 to plus 35%) as compared with 9 points (from plus 43 to plus 34%) for 1.5 mg., 14 points (from plus 40 to plus 26%) for 3 mg., and 27 points (from plus 36 to plus 19%) for 6 mg. Whereas the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most hospital patients with exophthalmic goiter in Boston is about 6 mg. per day, the smallest amount that will produce any effect is greater than 0.75 mg. per day in about two-thirds of the cases, and is probably not much less than 0.75 mg. per day in the other third. Within these limits of dosage, there appears to be roughly a linear relationship between the percentage approach of the basal metabolism toward the normal level and the dose of iodine. It also appears that within these limits of dosage the reduction in basal metabolism is roughly proportional to the amount of iodine available for the storage of colloid. In five of 46 patients who received from 0.75 to 3 mg. of iodine daily, the reaction to iodine appeared to be reversible; i.e., the basal metabolism rose during the administration of the small dose and fell during the immediate subsequent administration of a much larger dose. Iodine must be supplied to the thyroid gland at a certain minimum rate in order for the maximum effect to occur.—W. O. Thompson.

Menorrhagia due to hypothyroidism. Waters, W. C. and G. A. Williams, Am. J. Obst. & Gynec. **23**: 489. 1932.

In 6 cases of menorrhagia the subjects were found to exhibit symptoms of hypothyroidism. All complained of weakness and sensitiveness to cold and had some degree of dryness of the skin. The nutrition of these patients varied greatly and the basal metabolic rate ranged from 105 to 78% of normal, with a mean of 88%. The excessive bleeding in all cases was controlled by proper doses of thyroid substance.—W. Waters.

The effects of prolonged administration of potassium iodide in rabbits. Westra, J. J., Proc. Am. Physiol. Soc. P. 98. 1933.

The purpose of this investigation was to compare the effects of prolonged daily administration of potassium iodide to adult and to growing rabbits. Oral administration of potassium iodide (in capsules) in amounts of 0.1 gram per day caused a marked loss of body weight, and finally caused death of the animal. The animals showed a terminal cachexia, diarrhea, and rise in body temperature. At autopsy there was enlargement of the adrenals, and frequently hyperemia of the lungs and pleural effusion. When potassium iodide is administered orally in increasing doses to growing rabbits, a dose of 1.4 grams per day may finally be given with no effect on body weight when compared with that of litter-mate controls. The thyroid at autopsy is hard with decreased vascularity, and microscopically shows a flattened epithelium with an increased amount of colloid. This microscopic picture may also be found in some control animals. Growing rabbits injected subcutaneously with isotonic potassium iodide solution in increasing doses may finally be given 2.5 grams potassium iodide daily without showing any differences in weight when compared with litter-mate controls injected with an equivalent dose of potassium chloride.—Author's Abst.

The influence of pregnancy upon the calorigenic action of thyroxine. Wilhelmj, C. M., S. L. Moskowitz and I. Neigus, Proc. Am. Physiol. Soc. P. 99. 1933.

The calorigenic action of 10 mg. of thyroxine administered intravenously has been studied in the same dog before, during and after pregnancy. Because of variations in the level of the basal metabolism the responses were calculated from the zero base line in all curves, thus giving the "total" rather than the "extra" response. In general, however, the extra response showed the same variations as the total. Four experiments performed before pregnancy gave an average value of 808 liters of oxygen with maximal and minimal variations of $\pm 4\%$. The duration of the response was approximately one week. Experiments starting on the 36th and 58th days of pregnancy gave values of 997 and 1203 liters of oxygen, respectively. This increase in the calorigenic action of thyroxine persists during the early post partum period and was 972 and 977 liters in experiments beginning on the 4th and the 25th days post partum. The individual curves show that the calorigenic action is more sustained and of longer duration than before pregnancy. The increase is not due entirely to the lengthening of the curves since it is still definitely increased when calculated for a period of one week. The response finally returns to normal so that on the 166th and 195th days post partum the values were again within the range obtained before pregnancy. During the early part of pregnancy there seems to be a slight drop in the B.M.R. followed by a rise in the latter part. After parturition the B.M.R. showed a profound drop and required approximately 6 months to return to normal. Since the increase in the calorigenic action of thyroxine persisted into the post partum period it is not due to fetal influences. As a working hypothesis we suggest that these results are due to a relative reduction of the thyroxine concentration in the body of the mother. Further work is in progress.—Authors' Abst.

The calorigenic action of thyroxine in normal dogs and a comparison with the response in human subjects. Wilhelmj, C. M. and I. Neigus, Proc. Am. Physiol. Soc. P. 100. 1933.

Wilhelmj and Boothby noted the constancy of the calorigenic action of 10 mg. of thyroxine when administered intravenously in the same dog maintained under standard conditions. In the present study we have analyzed the response in two different dogs and compared it with the response of the human subject. Five experiments were performed on Dog I (reported by Wilhelmj

and Boothby) which weighed 7.4 kg.; six experiments were performed on Dog II which weighed 11.1 kg. The averaged extra oxygen consumption following the intravenous injection of 10 mg. of thyroxine was 73 liters for Dog I and 102 liters for Dog II. In both dogs the maximum and minimum variations from the average were within ±10%. In a comparative study of these results it was found that an almost perfect agreement was obtained when the calorigenic action was expressed as liters of extra oxygen per kilogram of body weight per mg. of thyroxine; this value averages 0.99 liter in Dog I and 0.92 liter in Dog II. This value was compared with the value obtained on three human subjects reported in the literature and was found to be approximately the same. Fourteen experiments on two dogs and three human subjects gave an average value of 1.05 liter of extra oxygen per kilogram of body weight per mg. of thyroxine and the maximum and minimum variations were within ±12% of the average. From this it appears that the calorigenic action of thyroxine in dogs and human subjects is practically identical when expressed in this manner.—Authors' Abst.

The use of iodine in the pre-operative treatment of hyperthyroidism; with remarks on iodine remissions as observed in Baltimore. Winkenwerder, W. L. and D. McEachern, Bull. Johns Hopkins Hosp. **51**: 282. 1932.

The data on 157 subjects of hyperthyroidism treated with iodine are analyzed and presented. The division of the series into the exophthalmic type and nodular goiter with hyperthyroidism was not made because features of each type were observed frequently in the same patient. One hunded and forty-four cases responded with definite iodine remissions, the point of maximum improvement being reached on or between the 8th and 32nd days; the greatest number reached this point on the tenth day; the average for the entire series was 13.5 days. As a rule, mild cases presented their remission one or two days earlier than the more severe. An average decrease of 50% in the metabolic rate was obtained regardless of its initial level prior to iodine therapy. These studies correspond closely to the series reported by Means and others from Boston, except that in the latter city remissions were reached one or two days earlier; in contrast, however, the series from Michigan, a goitrous area, reported by Coller and Potter, responded less favorably than either the Boston or Baltimore cases. No essential difference between subjects of exophthalmic goiter and nodular goiter with hyperthyroidism in their reaction to iodine was noted. Of the 14 cases of the latter type, included in the general series, 13 showed remissions similar in rate and degree to those exhibited by the entire series. This fact, coupled with observations reported from other clinics of the country, strengthens the growing conception that only one type of hyperthyroidism exists, and that typical remissions with iodine in the majority of instances can be obtained in the nodular group as well as in the exophthalmic type. Several reactions to iodine are illustrated: (1) Slow prolonged improvement; (2) reappearance of signs and symptoms of the disease during prolonged administration; (3) two consecutive remissions occurring in the same patient with only a short inter-iodine period (2 weeks); (4) iodine—the final pre-operative therapeutic agent; (5) exacerbation of the disease coincident with iodine administration. Because of the temporary nature of the iodine remission, emphasis is placed on the advisability of administering iodine according to a definite course with operation almost without exception definitely in mind. A preliminary pre-iodine period of general medical care, it is believed, will produce a greater ultimate improvement than that obtained by iodine alone. There is increasing evidence to the effect that iodine should be restricted with few exceptions to the pre-operative preparation of the patient. The dosage of iodine and the various forms in which it may be given are commented on.
—Authors' Abst.

Proof of a glycogen test for the indication of thyroxine in the blood of hyperthyroidized dogs (Prüfung eines Glykogentestes zum nachweis von Thyroxin im Blute hyperthyreoidisierter Hunde). Wittgenstein, A., Arch. f. d. ges. Physiol. **229**: 299. 1932.

The author injected male mice with blood serum, thyroxine or other substances and tested the liver for the presence of glycogen. In a few cases the mice were tested against acetonitrile. Normal human or dog blood gave no effect on the liver glycogen. Injection of the thyroid hormone, blood from Basedow cases, blood from pregnant women, and blood from hyperthyroid dogs gave negative tests for liver glycogen.—B. O. Barnes.

Normal and pathologic repair in the thyroid gland. Womack, N. A. and W. H. Cole, Arch. Surg. **23**: 466. 1931. Author's Abst., J. Nerv. & Ment. Dis. **75**: 675.

Increase in the functional activity of the thyroid gland is extremely common and is dependent on a number of factors. This increase in function is usually associated with definite morphologic, chemical, and physiological changes that may occur to an extreme degree. If the stimulus is great enough, these changes may take place during the course of a few hours. A more or less mild stimulation of the thyroid gland over a relatively long period of time may produce hyperplastic changes similar to those seen in exophthalmic goiter. Following involution brought about by the disappearance of the stimulus, causing the increase in function, or by artificial involution due to the administration of iodine, replacement of fibrous tissue occurs. Repetition of this physiologic cycle may produce a nodular goiter similar to the so-called adenoma. The occurrence and location of these nodules is apparently dependent on the amount and location of the fibrosis. Experimental evidence is offered in support of these facts. The thyroid stimulation was brought about by the use of certain types of infection and by drugs, over varying periods of time.

The effect of cabbage feeding on the morphology of the thyroid of rabbits. Zeckwer, I. T., Am. J. Path. **8**: 235. 1932. Abst., Ann. Int. Med. **6**: 451.

Feeding winter cabbage in the early part of 1931 to 17 rabbits for periods up to 114 days produced hyperplasia of the thyroid, but in only two instances were enlargements to more than twice the normal weight obtained. The microscopic changes were more conspicuous than the gross enlargement. The data obtained support the view of Webster, Marine and Cipra that there is an annual variation in the goitrogenic agent in cabbage, as well as seasonal differences and differences in the susceptibility of individual rabbits.

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